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CONTENTS OF VOLUME 84

JULY 1949 NUMBER 1

SIR WILLIAM OSLER MEMORIAL NUMBER

	PAGE
Frontispiece	
Editorial William Osler	1
The Medical Arena in the Toronto of Osler's Early Days in the Study of Medicine Norman B Gwyn, M D, Toronto, Canada	2
Osler's Original Autopsy Books H E MacDermot, M D, F R C P (C), Montreal, Canada	7
William Osler "A Potent Ferment" at McGill R Palmer Howard, M D, Montreal, Canada	12
Photographs Life of Dr Osler	16
William Osler in Philadelphia, 1884-1889 Francis R Packard, M D, Phila- delphia	18
Additional Notes on Osler in Philadelphia Edward B Krumbhaar, M D, Philadelphia	26
The Jocular Side of Osler George Blumer, M D, San Marino, Calif	34
Dr Osler's Renal Stones Thomas B Fitcher, M D, Baltimore	40
The Gay of Heart Thomas S Cullen, M D, Baltimore	41
William Osler A Personal Note James B Herrick, M D, Chicago	46
Dr Osler's Use of Time George Dock, M D, Altadena, Calif	51
Dr Osler Scientist and Teacher Rufus Cole, M D, Mount Kisco, N Y	54
Photographs Life of Dr Osler	64
Excerpts from Osler A Mosaic of Bedside Aphorisms and Writings William Bennett Bean, M D, Iowa City	72
Osler Recollections of an Undergraduate Medical Student at Johns Hopkins Henry A Christian, M D, Brookline, Mass	77
My First Medical Clinic with Dr Osler James E Paullin, M D, Atlanta, Ga	84
Aequanimitas Joseph H Pratt, M D, Boston	86
Random Recollections of William Osler, 1899-1918 Warfield T Longcope, M D, Lee, Mass	93
Hero Worship Wilder Penfield, M D, Montreal, Canada	104
Sir William Osler Reminiscences Wilburt C Davison, M D, Durham, N C	110
Photographs Life of Dr Osler	129
Osler at Oxford Sir Arthur S MacNalty, K C B, M D, F R C P, London, England	135
A Day with Dr Osler in Oxford Walter L Bierring, M D, Des Moines, Iowa	143
William Osler, the Humanist John F Fulton, M D, New Haven, Conn	149
Pathogenesis of Renal Lesions in Bright's Disease Arthur W M Ellis, M D, F R C P, Oxford, England	159

JULY—Continued

	PAGE
Posthumous Tributes to Sir William Osler E Rosencrantz, M D, San Francisco	170
"Front Door at the Back"	198

AUGUST 1949 NUMBER 2

Gastroscopic and Histologic Appearance of the Gastric Mucosa Before and After Vagotomy for Peptic Ulcer Joseph B Kirsner, M D, Eleanor M Humphreys, M D, Lester R Dragstedt, M D, and Walter Lincoln Palmer, M D, Chicago	199
Hysterical Type of Nongaseous Abdominal Bloating Walter C Alvarez, M D, Rochester, Minn	217
Medical Aspects of Submarine Warfare The Human Factor as Reflected in War Patrol Reports Commander Ivan F Duff, Medical Corps, United States Naval Reserve, Ann Arbor, Mich	246
Traumatic Coronary Thrombosis with Myocardial Infarction Postmortem Study Hyman Levy M D, New York	261
Chronic Nonleukemic Myelosis Report of Six Cases Clarence Merskey, M D, M R C P (London), Capetown Union of South Africa	277
Chronic Ulcerative Colitis and Carcinoma Joseph Felsen, M D, and William Wolarsky, M D, New York	293
Survival After Recent Myocardial Infarction L N Katz, M D, and G Y Mills, M D Chicago, and F Cisneros M D, Mexico D F, Mexico	305
Progress in Internal Medicine	
Gastroenterology A Review of the Literature from July 1947 to July 1948 (To Be Continued) Joseph B Kirsner, M D, Walter Lincoln Palmer, M D, William E Ricketts, M D, Julian W Buser, M D and Homer C Marshall, M D, Chicago	321
News and Comment	355
Book Reviews	357

SEPTEMBER 1949 NUMBER 3

Clinical and Biochemical Study of Remissions in Nonspecific Arthritis Report of a Case Benjamin H Archer, M D, New York	361
Barbiturate Poisoning Report of Three Cases Lloyd D Maver, M D, and Irving Greenfield, M D, Pittsburgh	379
Aerosol and Micronized Ephedrine and Penicillin Therapy of Diseases of the Lower Respiratory Tract Treatment of Bronchitis, Bronchiectasis and Intrinsic Asthma Samuel I Weinberg, M D, and George L Packer, M D, Los Angeles	389
Reflex Vasodilatation by Body Heating in Diagnosis of Peripheral Vascular Disorders A Criticism of Methods R H Goetz, M D, Ch B, and F Ames, M B, Ch B, Capetown, Union of South Africa	396
Familial Periodic Paralysis Report on Two Families, with Observations on the Pathogenesis of the Syndrome Dewey K Ziegler M D, New York	419
Clinical Syndrome of Occlusion of the Posterior Inferior Cerebellar Artery Report of Three Cases Burton Levine, M D, Louis J Cheskin, M D, and Irving L Applebaum, M D, Newark N J	431

SEPTEMBER—*Continued*

	PAGE
Relation of Pulmonary Embolism to Peripheral Thrombosis J M Spitzer, M D , Norman Rosenthal, M D Murray Weiner, M D , and Shepard Shapiro, M D , New York	440
Pericious Anemia in Early Adolescence Report of a Case in a Girl of Fourteen Henry E Hamilton, M D , and Willis M Fowler, M D , Iowa City	445
Progress in Internal Medicine	
Gastroenterology A Review of the Literature from July 1947 to July 1948 (Concluded) Joseph B Kirsner, M D , Walter Lincoln Palmer, M D , William E Ricketts, M D , Julian W Buser, M D , and Homer C Marshall, M D , Chicago	449
News and Comment	520
Book Reviews	521

OCTOBER 1949 NUMBER 4

Symptoms Attributable to Cold Hemagglutination Report of Two Cases Jeanne C Bateman, M D , Washington, D C	523
Ulcer of the Pyloric Ring Report of Twenty Cases George A Boylston, M D , Portland, Ore	532
Spontaneous Rupture of Syphilitic Saccular Aneurysms of the Ascending Aorta into the Pericardial Cavity, with Hemopericardium Report of Sudden Death in Twenty-Nine Cases Philip Goldstein, M D , New York	540
Dissecting Aneurysms of the Aorta Jakub G Schlichter, M D , George D Amromin, M D , and A J L Solway, M D , Chicago	558
Hematologic Studies in Hiroshima and a Control City Two Years After the Atomic Bombing Fred M Snell, M D , Boston, James V Neel, M D , Ph D , Ann Arbor, Mich , and K Ishibashi, M B , Hiroshima, Japan	569
Clinical Significance of Bacteroides Paul M Beigelman, M D , and Lowell A Rantz, M D , San Francisco	605
Myocardial Infarction Observations on One Hundred Patients Who Survived up to Six Years G Y Mills, M D , A J Simon, M D , F Cisneros, M D , and L N Katz, M D , Chicago	632
Intravenous Catheterization of the Heart in Suspected Congenital Heart Disease Report of Seventy-Two Cases Don W Chapman, M D , David M Earle, M D , Lloyd J Gule, M D , Russell A Huggins, M D , and Walter Zimdahl, M D , Houston, Texas	640
Book Reviews	660

NOVEMBER 1949 NUMBER 5

Role of Blood Platelets in Thromboembolism Sylvan E Moolten, M D , Leo Vroman, Georgine M S Vroman and Betty Goodman, New Brunswick, N J	667
Concepts of Myocardial Ischemia Hans H Hecht, M D , Salt Lake City	711
Excretion of Choline in the Urine of Diabetic Patients Tihamér Z Csaky, M D , Jakob Mollerstrom, M D , and Otakar V Šírek, M D , Stockholm, Sweden	730
Multiple Hemorrhagic Sarcoma and Diabetes Mellitus Review of a Series with Report of Two Cases Wilbur B Hurlbut, M D , and Charles S Lincoln Jr, M D , New York	738

NOVEMBER—*Continued*

	PAGE
Clinical Manifestations of Carrion's Disease William E Ricketts, M D , Chicago	751
Hepatitis and Its Sequelae, Including the Development of Portal Cirrhosis Observations on One Hundred Cases Michael F Koszalka, M D , M C F Lindert, M D , Herbert M Snodgrass, M D , and Harry B Lerner, M D , Milwaukee	782
Defect of the Ventricular Septum Summary of Twelve Cases and Review of the Literature Arthur Selzer, M D , San Francisco	798
Phytobezoar in the Gastric Stump Report of a Case and Discussion of Therapy L Walk, M D , Eskilstuna, Sweden	824
News and Comment	836
Book Reviews	838

DECEMBER 1949 NUMBER 6

Tussive Syncope Observations on the Disease Formerly Called Laryngeal Epilepsy, with Report of Two Cases William S McCann, M D , Robert A Bruce, M D , Frank W Lovejoy Jr, M D , Paul N G Yu, M D , Raymond Pearson, M D , Ernest B Emerson, M D , George Engel, M D , and John J Kelly, M D , Rochester, N Y	845
Aureomycin Treatment of Pneumococcic Pneumonia Clinical and Laboratory Studies on Thirty-Three Patients Thomas M Gocke, M D , Harvey S Collins, M D , and Maxwell Finland, M D , Boston	857
Aureomycin Therapy of Nonpneumococcic and Nontuberculous Bacterial Pulmonary Infections Harvey Shields Collins, M D , Thomas M Gocke, M D , and Maxwell Finland, M D , Boston	875
Sternal Marrow in Patients with Metastatic Cancer Patricia Farnsworth Lamer, M D , St Louis	891
Motor Manifestations of Herpes Zoster Report of a Case of Associated Per- manent Paralysis of the Phrenic Nerve Seymour Lionel Halpern, M D , Boston, and Albert H Covner, M D , Lynn, Mass	907
Q Fever in a Veterans' Hospital R W Brawley, M D , and F W S Modern, M D , Van Nuys, Calif	917
Pathology of Subchronic Atrophy of the Liver Comparison with Laennec's Cirrhosis Mogens Bjørneboe, M D , and Flemming Raaschou, M D , Copenhagen, Denmark	933
Anemia Associated with Cirrhosis of the Liver Study of Thirty-Two Cases Dr Keh-Wei Huang and Dr Herng-Wen Wang, Chengtu, China	958
Development of Porphyria in Diabetes Mellitus Report of Three Cases Kenneth Sterling, M D , Marvin Silver, M D , and Henry T Ricketts, M D , Chicago	965
Multiple Myeloma with New Bone Formation Philip Kramin, M D , Carl J D'Angio, M D , and Ammiel Smelin, M D , New York	976
Periarteritis Nodosa Study of Chronicity and Recovery, with Report of Two Cases Sander Paul Klein, M D , Detroit	983
Coronary Heart Disease and Xanthoma Tuberosum Associated with Heredi- tary Hyperlipemia Study of Thirty Affected Persons in a Family Rev M Alvord, M D , Salt Lake City	1002
Book Reviews	1020
General Index	1025

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NUMBER 1

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Editorial

WILLIAM OSLER

The ARCHIVES OF INTERNAL MEDICINE is deeply grateful to William Osler. His pen never contributed directly to our columns, yet the members of the first Editorial Board, Richard Cabot of Boston, George Dock of Ann Arbor, Mich., David Edsall of Philadelphia, Theodore Janeway of New York, Joseph Miller of Chicago and William Thayer of Baltimore, were guided by his teachings and literary skill in forming our editorial policies. The first volume, also, reflects his influence. Gifted physicians like Harlow Brooks, Louis Hamman and Francis Peabody, with many others who admired Osler's writings, were among the earliest contributors and helped to establish our most important aim—that the ARCHIVES be a monthly journal dealing with internal medicine in its broadest sense, and composed in such fashion that each article printed in it is instructive, well written and worth reading.

During the forty-one years that our periodical has existed, Osler's name has been referred to repeatedly by many authors in their manuscripts. Without question, the development of internal medicine in this country during the past half century, as traced in the ARCHIVES, has been notably colored by his personality. It is especially appropriate that this journal, devoted to internal medicine and published by an association representing the medical men of this country, should thus honor the man who brought so much honor to American medicine.

Osler's skill as a clinician, his ability as a "teacher and leader of men," his learning, his contributions, not only to medical science but also to literature, through many essays reflecting a broad culture and a sympathetic understanding of men and events—all have set an example of scholarly achievement and have been a source of inspiration to physicians everywhere.

For these reasons, the Editorial Board proudly dedicates this number to him in celebration of the hundredth anniversary of his birth, and as a salute to his memory.

The Editorial Board wishes to express a deep sense of gratitude to the former students and associates of Dr. Osler, and to all others who have made this memorial issue possible.

The Editorial Board
ARCHIVES OF INTERNAL MEDICINE

THE MEDICAL ARENA IN THE TORONTO OF OSLER'S EARLY DAYS IN THE STUDY OF MEDICINE

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TORONTO, CANADA

THE TITLE implies that more will be said of the conditions concerning medicine as practiced and taught in Toronto in the latter part of the last century than of Osler himself. The word "arena" well describes what Osler, at the beginning of his medical career, looked on as a student in the Toronto School of Medicine, for conflict of a most dramatic sort between the two medical schools of the city and their adherents had long been the order of the day.

One takes for granted that bickerings, quarreling and jealousies existed everywhere in the conducting of the medical institutions which rose and fell in the early days of the last century, but in Toronto, behind these lesser evils, there loomed large bitter hostilities grounded in colonial mismanagement, religious intolerance and armed rebellion against the government, culminating in discontent and, finally, in secession of the whole faculty of the one school then existing, to create a school of their own, which was to take the title of the school from which they had seceded. Of a less dramatic nature than these upheavals, yet adding to the envy, hatred and malice on the medical scene, was the eventual abolition of the Medical Faculty of the University of Toronto, as a teaching institution. The action was ascribed, although unjustly, to a remarkable character high in government circles, the Honorable John Rolph, M D, who was said to fear that his own medical institution, the original Toronto School of Medicine, would never be able to compete with the university faculty organized and conducted by the Provincial authorities.

In one of Osler's farewell addresses to the medical men of this continent,¹ one notes his affectionate references to his associations in Montreal, Philadelphia and Baltimore. No mention is made of his life in Toronto, yet Osler was for two years a student in the second Toronto School of Medicine, and his earliest known Canadian publication² is described as the work of W. Osler of the Toronto School of Medicine.

1 Osler, W. Unity, Peace and Concord, Oxford, H. Hart, 1905.

2 Osler, W. On Canadian Diatomaceae, Canad. Naturalist, N. S. 5: 142-151, 1870, Reprinted in Osler, W. Published Memoirs and Communications, Montreal, 1882.

An omission of this sort surely suggests that what Osler saw in his Toronto days was not too pleasing to his peace-loving nature. His intimacy with James Bovell and Rev. W. A. Johnson however, effectively removed him from the unpleasing surroundings which had evolved from the conditions mentioned. Most of Osler's reference to his Toronto days have to do with his association with Bovell. In 'The Master Word in Medicine' - an address delivered in Toronto in 1905 he merely greeted some of his old teachers present in the audience: Osler could doubtless well remember that some of these same old teachers had actively fomented strife during his student days. The Master Word in Medicine however may well be looked on as Osler's notification to the medical world that the unhappy state of affairs which had existed in the medical circles of Toronto in his student days was now a thing of the past.

For twenty-five years previous to Osler's entering on his medical studies there had been unending and vitriolic strife between the schools and their adherents a strife based on distinctly unusual happenings. As a rule the main object of the hostilities was the pioneer in the teaching of medicine in the Upper Province, John Rolph reformer, protestant rebel a fugitive with a price on his head, yet a great teacher and one able to build up a school of his own the first Toronto School of Medicine, after his return from a seven year banishment. Whether he was the old Shimei mentioned by Osler is perhaps questionable for in many ways he seems to have been more sinned against than sinning. Yet his name is closely associated with all the interesting happenings which preceded the breakdown of the teaching of medicine in Toronto.

A detail of colonial mismanagement may well appeal to American readers. In the early colonial days the governors of the Upper Province were the old type of aristocratic military men who had been brought up in England to believe that the State church the Church of England was the one and only religious organization to be given any consideration. Into the hands of the authorities of the Church of England in Canada was to be given the control of all education and to provide for the upkeep of the Church one seventh of all the arable land in the Upper Province was to be set aside. It apparently had never occurred to the governors and their advisers that, though the Church of England was the state-endowed church in England, such was not the case in Canada. All the religious bodies not so favored as the Church of England sooner or later protested this setting apart of land for the Church ('the Clergy Reserves'), and foremost in opposing the governors and the dictatorial Bishop Strachan of Toronto was John Rolph. His indictment of the

3 Osler W. The Master Word in Medicine. Oxford. H. Hart, 1905.

4 "One old Shimei in a community may cause dissensions which it will take three generations to remove."

Bishop and his associates, a classic in the records of the House of the Assembly, went far toward making the Colonial Office take notice of what was going on. The Clergy Reserves were taken from the Church of England, and the income from them was applied to the growing educational institutions of the province, without preference for any one sect. By his stand against the Bishop and the Church, Rolph at once incurred the enmity of the whole Anglican community, an enmity which gathered force as time went on.

The testimony of the superintendent of the Toronto General Hospital, in an investigation into conditions there in 1855 (an investigation provoked by complaints of Rolph's students that they got no fair treatment in the hospital and wards), shows to what extent religious intolerance could reach (at that time the Trinity College Medical Faculty, headed by James Bovell, seems to have assumed almost complete control of the hospital, the superintendent, Dr. Clark, was accused of favoring Trinity College).

Dr. Clark: "I will always support Trinity College, because it was my Alma Mater in the old country, and more than that, it is a college founded on the religion I profess, the Established Church of England, and I am not ashamed to confess my partiality for that church."

Mr. Bowes: "I don't think that because Trinity College is founded upon the religion you profess, that therefore you should show any partiality in this institute."

Dr. Clark (warmly): "That is another thing, sir. I consider the Medical Staff of Trinity College the most efficient in Upper Canada. I consider it the most perfect staff in Upper Canada, for this reason: every chair is filled by a professor who is admitted by the students of all schools to be an able man."

Reform and the struggle for responsible government in the Upper Province brought Rolph aggressively forward. He was one of the leaders in the abortive rebellion in which an attempt was made to capture Toronto and other towns. With its failure, Rolph had to flee the country, with a price on his head, and eventually settled in Rochester, N. Y. His association with the rebels naturally made him a person much to be hated by the ultraloyalist element. He remained, however, the idol of the reformists, and it is interesting that many Canadian students came to study with him while he was in Rochester.

After a term of banishment which lasted seven years, Rolph was pardoned, he returned to Toronto and at once began to teach medicine and to build up a school of his own, the first Toronto School of Medicine. Eventually, his school became affiliated with the Methodist university, Victoria College. This association, naturally, did not endear him to the Anglican part of the community, and in those days the members of the Church of England could not have been said to be tolerant of any sect which disagreed with them.

The Rolph school enjoyed an uninterrupted existence up to 1856, when signs of rebellion against his authority began to be evident among his six associates. On the opening day of its term, in October, they walked out of his institution, claiming that the will of the majority of the incorporators in an incorporated body could settle questions of ownership. They appealed to the courts, the courts decided in their favor and they were given the permission to use the title of the Toronto School of Medicine. Rolph quickly reestablished his faculty, but the fighting between the two schools became vicious to a degree. Most of the trouble which eventually developed in the medical world of Osler's time depended on this dramatic secession of Rolph's associates to form the new Toronto school.

One event, of a less dramatic nature than some, had added to the general hostility toward Rolph. This was the abolition of the Medical Faculty at the University of Toronto as a teaching institution. Rolph had become an active politician, in addition to conducting his medical school and, at the time of the abolition of the University Medical Faculty, had become Minister of Crown Lands. The members of the faculty at once raised the cry that Rolph had used his position as Minister to urge this abolition, in order that his own school might have a monopoly of the teaching of medicine in the Upper Province. What had really taken place, however, was that the University of Toronto was merely following the example of the University of London in deciding to give up the teaching of medicine and law while retaining the degree-conferring capacity.

The investigation of affairs in the Toronto General Hospital produced but little in the way of good results. It was only too evident that Rolph's association with these events had created such a host of enemies that he would find it difficult to obtain help from any direction. He and his staff were made unwelcome in the hospital wards, and his students even complained that they were unjustly dealt with in the state board examinations when they came before an examiner who was not of Rolph's persuasion. Nevertheless, Rolph fought valiantly to the end, finally retiring in 1870. He had been associated with the teaching of medicine since 1824.

There could have been only one ending to these manifold evils, a forecast appeared in one of the Toronto dailies of the time. "The bickerings of the profession are a by-word if not a hissing amongst us, you can hardly get half a dozen men allied to rival schools to come together for any common purpose." In spite of this castigation, matters in the medical world went from bad to worse, dissension among the doctors was finally reflected in the closing of the Toronto General Hospital, the one institution in the city in which clinical medicine could be

taught in 1868-1869 Most clear-thinking students migrated to McGill, or elsewhere, Osler followed later, in 1870, knowing by then that his friend Bovell was not planning to return to Toronto from the Barbadoes There could now be no attraction for Osler in Toronto's medical world

When the hospital reopened, it was with only twenty-five beds to provide clinical teaching for two schools The governors, in a report, reprimanded the visiting staff severely for many delinquencies and complimented the migrating students on the step they had taken With the reopening, however, and a reorganization of the medical schools, as demanded by the governors of the hospital, an element of peace became evident, to be added to shortly by the retirement of Dr Rolph, now well advanced in years, and by the decline and disappearance of his medical school, then attached to Victoria College A final note of tragedy in the life of the old fighter was that a new building, provided for him and the school by Victoria, was to be occupied by his now successful rivals, the men who had seceded from his school some fifteen years before

These, then, were the scenes and events which confronted the young Osler when he began his medical studies in the second Toronto School of Medicine It cannot have been with any great enjoyment that he listened to the recriminations passing between the two schools, nor can he have enjoyed the constant baiting of Rolph, who, after all, had been a real reformer and a fighter against many evils Further, with Bovell not returning to Toronto, there cannot have been much inducement to keep him in the Toronto school Thus, Toronto lost Osler, the most promising student of the time, while McGill University acquired an enthusiast in the study of medicine whose name was to spread far, and whose influence was to be worldwide

OSLER'S ORIGINAL AUTOPSY BOOKS

H E MacDERMOT, M D, F R C P (C)
MONTREAL, CANADA

ONE of the best documented figures in medicine, William Osler, raised his own literary monument, and it was further adorned by the personal tributes so freely outpoured in his memory, then, all received the final floodlighting of Cushing's biography¹ As it happens, the literature is extremely distracting for my object The more of it one reads, the longer one postpones the achievement of that "flighty purpose" which Osler was so eminently able to overtake

From the mass of literary scaffolding which has been discarded in producing Osler's memorials, I have chosen the manuscript books containing Osler's early autopsy descriptions Apparently, there were five, but only two have been preserved² Osler used all these books when he was writing his textbook in Baltimore, but when the missing ones went astray is not known

Of all the specimens of his own handwriting, few more vividly and directly remind one of Osler than do these notes They tell of his intense absorption in the aspect of medicine which, in his earlier years, certainly fascinated him beyond all others As Thomas McCrae said "Of the various ways of approach to clinical medicine there is no doubt as to the one by which William Osler travelled"³

The two books contain entries from May 4, 1877 to March 14, 1879, and from March 14, 1879 to Sept 12, 1880 Many descriptions are written in his own hand⁴, others, done by students from his dictation, often bear his corrections Probably some were written up from notes The books are in remarkably clean condition, considering the handling they must have had and the primitive conditions under which they were

1 Cushing, H Life of Sir William Osler, Oxford, Clarendon Press, 1926

2 These have been given to the Osler Library, Montreal, by the Montreal General Hospital

3 Sir William Osler Memorial Number, Bulletin 9, International Association of Medical Museums, Toronto, Murray Printing Co, Limited, 1926, p 37

4 Osler's writing was usually small and neat, but he often scribbled Dr W W Francis tells of an instance in which Osler wrote to a friend, asking to be informed on some point on "chancre," and adding that "Bill Francis" was much interested in this It was many years later that it was discovered that the word was "Chaucer"!

produced The autopsy room at the Montreal General Hospital was then little more than an outhouse, with a wooden table and a stove which was lighted only as required, and was not very effective even then One of Osler's students, George E. Armstrong,⁵ has told of lighting the stove on many occasions and warming a bucket of water for the work

At the time that the first of these books was produced, Osler had no regular appointment on the staff of the hospital He did the post-mortem work because he liked it, and when he was appointed full physician in 1878 (he was only 29 and spoke of his appointment as a "scandalous" elevation over the heads of his seniors), he went on with it, and the other men on the staff were only too glad to let him do most of their autopsies Frequently, in the notes, he speaks of a case as "Bell's" or "Roddick's"

It is hard to better the terse, graphic writing Many of the notes are in print in the first volume of the "Montreal General Hospital Reports" and in scattered reports in the journals of the day It is notable that the original descriptions, as dictated by Osler, needed hardly any editing for the printed version Here is a typical general description

Body that of a much emaciated, delicately built girl Hair lanky Skin rough and dry Fingers slightly clubbed and nails a little incurvated Bed sores on sacrum Left foot and ankle swollen and oedematous, right slightly so Chest narrow Ecchymoses—small and punctiform—in the region of the ensiform cartilage and scattered over the skin of the abdomen

While the cases were of great variety, two conditions predominated, since they contributed most to the mortality in the hospital at the time pulmonary tuberculosis and typhoid It is unlikely that Osler took any special precautions against infection at autopsy, except of course after pricking or cutting himself, and yet, even after repeated handling of extremely infectious material without gloves and with very crude water facilities, he escaped serious infection He did, however, acquire tuberculosis of the skin, in the form of "anatomical tubercles," as they were called He had eight or ten of these during fifteen years but did little more than watch them, recording that one took seven months to disappear

One has to remind oneself, in reading over the descriptions of cases of phthisis, that Osler was then as much in the dark about the tubercle bacillus as was Hippocrates One of his earliest descriptions is that of a Negro who died with a typical history (as it is now recognized) of acute pneumonic phthisis fever, cough, weakness, emaciation and a family history of tuberculosis Signs of cavitation were detected clini-

5 Armstrong, G. E., cited in Sir William Osler Memorial Number,³ p. 176

cally at the apex of the left lung, with evidence of consolidation at the bases. Cavities were present at both apices. Osler's comment was

This case is one which presents several points of great interest. Is it a sequence of pneumonia, or is the process tuberculous? The entire illness lasted somewhat over two months, and began after a wetting, but not with the symptoms of ordinary pneumonia. When he entered the hospital there was consolidation, with signs of breaking at the apex. The history is defective, and if the primary attack was pneumonic, it must have been subacute. A sister died of phthisis, so that a family predisposition to tuberculosis may be presumed.

I have never seen such an extensive area of cheesy degeneration as presented by the (left) lower lobe, uniform, solid, anaemic and dry, no trace of normal lung tissue (except narrow rim at border) and no nodules. In the upper lobe the walls of the cavity are formed by breaking down cheesy substance. The microscopical examination shows the air cells occupied with a granular debris, mixed with cells in various stages of degeneration.

The whole appearance is what might be supposed to proceed from an unresolved pneumonia, which had gone on to caseation, and in the upper lobe to extensive softening.

In all the early autopsies, he went into the minutest detail in describing various tuberculous cavities. He also paid great attention to the presence of adhesions in the pleural cavities, frequently underlining a note on them. In one report, after describing multitudes of cavities in both lungs, and caseous masses, he added, "There do not appear to be any *miliary* tubercles in the lungs."

But whatever his accounts may have lacked on account of bacteriologic gaps, his anatomic descriptions were so good that he was to use them unchanged many years later.

In typhoid he was on surer ground, though still without bacteriologic light. Here, too, he must have run great risks of infection, though evidently without ever acquiring the disease.

The very condition of the body at the time of autopsy must often have added to the work. There were no iceboxes then (once a body was noted as being "frozen"—this in December 1877), and sometimes there was a long interval between death and the postmortem examination. In a case of phthisis the autopsy was done eighty hours after death, and Osler made the note "Intestines and other organs of a greenish colour and smell powerfully." He then crossed out the word "powerfully," but the description was still carefully detailed.

His notes on the external aspect of the body were always thorough, now and then they tell us something of the treatment of the day. In a case of erysipelas, for instance, he wrote "Body that of an elderly, corpulent man. Hair scaly, grey. Left leg much swollen, oedematous, and covered over with flour, put on for the erysipelas", in another case, "On the thorax, the cicatrix of an old croton oil rash", and, again, "The whole of the left half of the chest behind is raw from the appli-

cation of a plaster " He added odd details A patient with pneumonia "had been a prostitute", a man with tuberculosis had the "letter D tatooed [sic] on left mammary region—old deserter from the A army", "lacteal vessels of the mesentery beautifully injected" (in a case of burns)

His similes were good He speaks of kidneys being "firm and cutting like a piece of turnip" He liked to be exact "Two supernumerary spleens, one kidney-shaped, the size of a plum, the other, round, the size of a cherry", again, "tricuspid orifice is small compared with the size of the right heart It admits three fingers to middle of 2nd joint (scarcely)", and, "the arch of the aorta admits the little finger of my right hand as far as root of nail"

He could not always obtain the organs "The chambers of the heart were dilated, and the walls hypertrophied (measurements not taken as the organ could not be taken away)" In a case of apoplexy, after carefully describing the brain and a large hemorrhage in the pons, he wrote

It was found impossible to trace any vessel specially diseased in the vicinity of the clot, nor on careful inspection could any aneurisms, military or otherwise, be seen Nothing could be "filched," so that a more thorough examination could not be made

Organs were often weighed, but not always Sometimes he had not time to finish the autopsy, and once he wrote

A very hurried examination made, without discovering anything except probably commencing cirrhosis of the liver, a portion of which was reserved for microscopical examination

One sheet of notes merely reads "Body well nourished On removing cerebral dur "

An occasional autopsy record has pinned to it a hospital slip, which now and then has a special note from the admitting officer (at that time Dr James Bell), asking Osler to hurry things up One note reads

Please come early Body must be removed by 4 o'clock tram and I want to put everything in order before friends arrive or there will be the d—— to pay

On another slip Dr Bell wrote

I have secured autopsy with much trouble and have pledged myself that they can have the body at 3 p m tomorrow without any visible sign of operation

A few of his terms are no longer used He spoke of the kidney capsule "detaching" easily Other examples are "the lower lobe in a condition of low pneumonia" and "apex occupied by large anfractuous cavity" He seemed to like this term, using it twice in successive autopsies, perhaps he was reading Boswell at the time! He wrote also of "patches of attrition" over the walls of the heart

A variety of clerks wrote from his dictation, but the initials of only one of them appear, "R L McD" (Dick McDonnell, who was a great favorite with Osler) Now and then the student's spelling became something notable, even for those days of careless spelling One wonders whether Osler was a little indistinct in dictating "Malpighian" was spelled "malpoghian" by one student and "Malpidgeon" by another But Osler could not be blamed for the following specimen

In the thorax the lungs do not colapse A large patch of atrition ova anterior surface of right ventrical Left auricle also contains groumous clots

In the right ventrical the columi carni are greatly developed, especially on the ceptum Artic valve presents large vegetations In left apex there is a purpel spot A considerable number of small miliary tubicles are scatered through this Only a few miliary tuburcles are noticed

Osler would often correct or add to the actual phrases, but he left the spelling alone His own was not above reproach now and then "latterally" and "peice" occur in his own handwriting

As might have been expected, the autopsy room intruded into Osler's dreams He left a record of a number of his dreams, Dr W W Francis⁶ tells of one, in which Osler was watching his own autopsy being performed at Oxford, in the presence of Dr William H Welch, of Baltimore, and Sir Clifford Allbutt

The pathologist, on opening Osler's heart, said "Yes, ängina pectoris," and Osler remarked, "That's right, X, whenever Welch or Allbutt is present I always say ängina" It was only when his intestines were all out and being cut up that Osler realised that he was permanently dead, and the shock woke him!

3640 University Street

6 Francis, W W, cited by Segall, H N First Clinico-Pathological Case History of Angina Pectoris, Bull Hist Med **18** 102, 1945

WILLIAM OSLER "A POTENT FERMENT" AT MCGILL

R PALMER HOWARD, M D
MONTREAL, CANADA

TO THIS day, William Osler is regarded as the most outstanding physician ever to be associated with the McGill Medical School. This may seem strange when it is recalled that he left Montreal at the age of 35. Actually, throughout his whole life he kept in close personal touch with his alma mater. Furthermore, several of Osler's former pupils became McGill professors, and two are still active teachers. Osler's influence remains a powerful factor at McGill. Every medical student is inspired by learning of his professional eminence, his enthusiasm for medical knowledge, his clinical abilities and his way of life, the memory of him has been of immeasurable benefit to the university. It is my particular wish to recall his vitality and his originality.

Before Osler's day the McGill Medical School had attained a prominence in Canada based largely on its clinical facilities, which were modeled on those of Edinburgh, where many of McGill's early leaders were trained. Above all, the school's standing was due to the emphasis given to bedside teaching, which had commenced as early as 1845, as was shown in the dean's historical review of the school on the occasion of its fiftieth anniversary, in 1882¹.

Because of these clinical opportunities William Osler came as a student to McGill in 1870. He brought with him an unusual knowledge of microscopy, which he had acquired under the Reverend William Johnson, at Trinity College School, and under Dr James Bovell, in the Toronto School of Medicine. His attainments in microscopy were

From the Department of Medicine, Montreal General Hospital, and McGill University

1 Howard, R P. A Sketch of the Life of G W Campbell, and a Summary of the History of the Faculty, Montreal, Gazette Printing Company, 1882.

Robert Palmer Howard, professor of the theory and practice of medicine at McGill in Osler's student days and dean of the Faculty from 1882 to 1889, was my grandfather. Such a personal bond of friendship existed between the two men that Osler was chosen in 1877 to be godfather to my father, Campbell Palmer Howard. In due time my father became one of Osler's housemen at Johns Hopkins Hospital, he was forever inspired by him. Osler's son, Revere, was my father's godson, and, in turn, was named my godfather, his untimely death as a combatant officer in the first world war put a sad end to this interlocking chain of devoted friendship and professional inheritance.

largely responsible for the award of a special prize for his graduation thesis in 1872. During his undergraduate years he had become closely associated as pupil, fellow student and personal friend with the professor of the theory and practice of medicine, Dr Robert Palmer Howard.

After two years' study in Europe, Osler returned to McGill as lecturer (later professor) of the Institutes of Medicine, which included physiology and pathology. He was also active in the Montreal General Hospital and became its first pathologist in 1876. Osler's abilities as a pathologist were rapidly recognized, and his reports to the local medical society were both frequent and original. That his innovations as a teacher of laboratory subjects were notable is attested by excerpts from the historical review given in 1882.¹

Instruction in the employment of the microscope in medicine forms a special summer course, and was begun in 1875. Another important advance was made in 1876, when the indefatigable Professor of Institutes began a series of weekly demonstrations in morbid anatomy. Finally, in 1879, a physiological laboratory was added to the technique of the chair of Physiology, and the senior students have now the opportunity of studying practically the essentials in the chemistry of digestion, the secretions and the urine, and of following a demonstration course in experimental physiology with the use of apparatus.

Thus, Osler's influence at McGill was felt first in its laboratories. He was also in close contact with all the students as registrar of the Medical School. Furthermore, in 1878, at the early age of 28, he was made an attending physician at the Montreal General Hospital. Once again the originality and vitality of his approach were evident, this time as a clinician. The words of Dr E. J. A. Rogers are quoted by Harvey Cushing.²

When therefore his time came to take charge of a section of the hospital, older doctors looked on with bated breath, expecting disastrous consequences. He began by clearing up his ward completely. All the unnecessary semblances of sickness and treatment were removed, it was turned from a sick-room into a bright, cheerful room of repose. Then he started in with his patients. Very little medicine was given. To the astonishment of everyone, the chronic beds, instead of being emptied by disaster were emptied rapidly through recovery, under his stimulating and encouraging influence the old cases nearly all disappeared, the new cases stayed but a short time. The revolution was wonderful. It was one of the most forceful lessons in treatment that had ever been demonstrated.

In 1884, to the great regret of his associates at McGill, Osler accepted the call to the chair of clinical medicine at Philadelphia. Frequent journeys to Montreal, to medical meetings elsewhere in Canada and also to the summer homes of such friends as Howard and the anatomist and surgeon Francis Shepherd, kept him in close contact with his associates.

² Cushing, H. Life of Sir William Osler, Oxford Clarendon Press, 1926, vol 1, p 172.

at McGill Strong efforts were made to attract him again to McGill University, first in 1892, when he was offered the professorship of medicine, and then in 1895, the principalship of the university But these temptations proved unavailing It is of interest that in 1902 he was asked to look over the plans for new buildings at the Montreal General Hospital Even in his later years at Oxford, his contacts with McGill men were kept fresh, and never more so than when his son Revere served in the McGill hospital unit and Sir William, with his many duties, became the honorary consultant to the Canadian Army Medical Corps

Osler's influence at McGill was spread not only by his former associates but also by younger men who had been his pupils at Baltimore and Oxford before becoming teachers at McGill All such men made frequent references to the man they regarded as the ideal teacher and model physician, so that successive groups of undergraduates were brought into contact with Osler's teachings Unfortunately, of his former pupils only Dr W W Francis and Dr Wilder Penfield remain active at McGill today

In medical societies, Osler was a leading light from his earliest days in Montreal The Montreal Medico-Chirurgical Society, at which many of his early papers were read, and the McGill Medical Undergraduate Society, which he helped to found, are still active organizations Osler's name is associated with two comparatively new societies, which originated after his death, but which carry on certain of his special interests The Osler Society was founded in 1921 by a group of undergraduates, for the special purpose of studying medical history At present the membership is unrestricted except in numbers, in which it is limited to about ten from each class Each member is expected to present at least one paper on a historical subject Under the able and friendly guidance of Dr Francis, the task becomes an experience gained and shared

There are three reporting societies at McGill, composed largely of the younger men on the teaching staff and entitled, the McGill, the Lafleur and the Osler Reporting Society Through these small groups, practicing physicians and specialists in various branches of medicine communicate recent advances to their confreres Osler can be imagined as an enthusiastic leader and critic at any such gathering

McGill is also fortunate in having the greater part of Osler's personal collection of medical books and documents in the Osler library It is located close to the main medical library, in a homelike suite of comfortably appointed rooms, and is under the curatorship of Osler's nephew, Dr W W Francis The visitor is ever impressed by this living memorial and cannot leave without receiving an enhanced stimulation

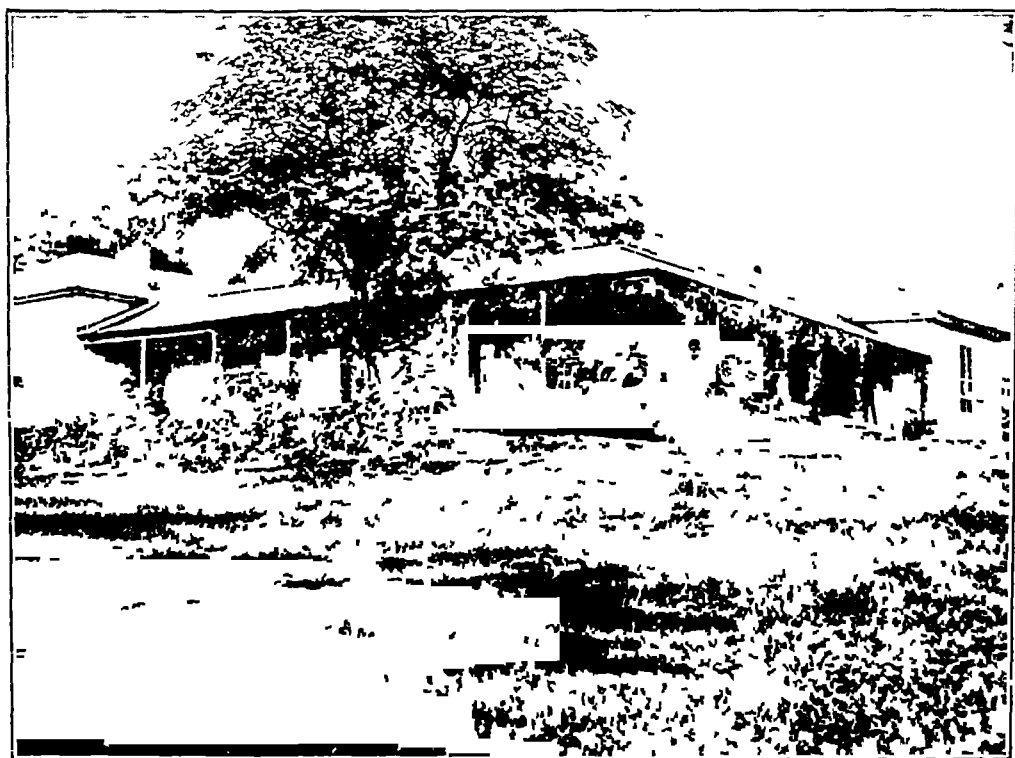
to study medical literature. The library is a treasure house of rare reference books and serves an important role as adjunct to the general medical library.

The accomplishments of Osler take a high place among the great traditions of the McGill medical school. Inspired by the traditions already present, he contributed to them much of his personality, his progressiveness and his enthusiastic energy. I can best illustrate the esteem in which he was held at McGill with the words written by Dr Howard in 1884, when Osler was considering the move to Philadelphia.³

The thought of losing you stuns us, and we feel anxious to do all that we can as sensible men to keep you amongst us, not only on account of your abilities as a teacher, your industry and enthusiasm as a worker, your personal qualities as a gentleman, a colleague and a friend, not only on account of the work you have already done in and for the school, but also because of the capabilities we recognize in you for future useful work, both in original investigation which shall add reputation to McGill and in systematic teaching of any of the branches of Medical Science you may care to cultivate, and finally because we have for years felt that vitalizing influence upon us individually exercised by personal contact with you—analogous to that produced by a potent ferment.

The memory of Osler is still a mainstay and an inspiration. Without it McGill would not be the same. But his life teaches us that we must not be constrained by traditional bonds. Just as Osler made innovations in the laboratories and wards in his day, so must we take up the tradition and freshen and reinterpret it in the light of the advances of our day. Let us look with respect to the past and yet continue to move forward under the vitalizing influence of "a potent ferment."

³ Cushing,² p. 224



Osler's birthplace, the Rectory, Bond Head, Tecumseh Parish, Ontario The figures are not Oslers, the family left in 1857, and the photograph was taken year later



William Osler (left), with three of his five brothers, his two sisters and five other neighbors, at Bond Head about 1854



Old tintypes A, Osler, about 1870, B, Osler, F J Shepherd and George Ross about 1878

WILLIAM OSLER IN PHILADELPHIA

1884-1889

FRANCIS R. PACKARD, M D
PHILADELPHIA

CUSHING¹ writes that Osler was abroad on one of his periodic "brain dustings" when he noted in his commonplace book on June 17, 1884 "Telegraphed Tyson from Leipzig that I would accept Professor of Clinical Medicine in the University of Pennsylvania, 'Yes' " In a letter to George Ross, written a few days later, Osler states that he had just received an unofficial letter from Dr James Tyson, at that time professor of pathology at the University of Pennsylvania, asking him if he would accept the appointment if selected, and that he had replied in the affirmative

Cushing gives Osler's own story of the matter as recounted in 1916, before a club of American Rhodes Scholars at Oxford

I was resting in a German town when I received a cable from friends in Philadelphia, stating that if I would accept a professorship there I should communicate with Dr S Weir Mitchell who was in Europe and who had been empowered to arrange the details I sat up late into the night balancing the pros and cons of Montreal and Philadelphia In the former I had many friends, I loved the work and the opportunity was great In the latter the field appeared very attractive, but it meant leaving many dear friends I finally gave it up as unsolvable and decided to leave it to chance I flipped a four-mark silver piece into the air 'Heads I go to Philadelphia, tails I remain in Montreal' It fell 'heads' I went to the telegraph-office and wrote the telegram to Dr Mitchell offering to go to Philadelphia I reached in my pockets to pay for the wire They were empty My only change had been the four-mark piece which I had left as it had fallen on my table It seemed like an act of Providence directing me to remain in Montreal I half decided to follow the cue Finally I concluded that inasmuch as I had placed the decision to chance I ought to abide by the turn of the coin, and returned to my hotel for it and sent the telegram

Osler already knew many of the leading members of the medical profession in Philadelphia On at least one occasion, he had visited the city and seen something of William Pepper and James Tyson, and he had also met other physicians at medical meetings Dr Minis Hays had asked him to serve as correspondent in Montreal for the *Medical News*, and he and Dr Samuel W Gross, of Philadelphia, had been fellow delegates to an international congress in London in 1881 (While in England, Dr and Mrs Gross had visited Sir Henry Acland, Regius

1 Cushing, H Life of Sir William Osler, Oxford, Clarendon Press, 1926

Professor of Medicine at Oxford, at his home, and Mrs Gross had noticed the panel portraits of Linacre, Harvey and Sydenham which hung over a mantel. She was to recall them vividly when, after Dr Gross died, she married Osler and he succeeded Sir Henry as Regius Professor, for he had copies of the panels hung in their Oxford home.) When the Grosses returned to Philadelphia, the elder Gross had asked them to tell him of some of the men they had met, and the younger Gross said that he had heard a swarthy young Canadian give one of the best papers of the congress, and he hoped that some day they might get him in Philadelphia.

The chair of clinical medicine in the University of Pennsylvania had been held by Dr William Pepper, and, when, in 1884, Dr Alfred Stillé resigned as senior professor of medicine, it was but natural and right that Dr Pepper should be elected his successor. There were several candidates to succeed to Dr Pepper's chair. Curiously enough, the suggestion of Osler's name came first from a group of men most of whom were not connected with the University of Pennsylvania. At a meeting of the editorial staff of the *Medical News* the matter was freely discussed, and surprise was expressed by some of those present that other names had not been considered. Those at the meeting were Drs Minis Hays, Roberts Bartholow, Theophilus Parvin, Samuel W. Gross and James Tyson, the last the only one officially connected with the university. Osler's name was mentioned, and Dr Tyson was urged by all present to bring it to the attention of the university. Tyson spoke to Dr Horatio C. Wood, then professor of therapeutics, who at once journeyed up to Montreal for firsthand information about Osler, whom he had never met. Dr Wood got such wonderful reports that he came back to Philadelphia full of zeal to secure Osler's appointment.

There was an amusing sequel. Dr S. Weir Mitchell had cabled to Osler to meet him in London, as he and Mrs Mitchell were commissioned to "look him over." Osler wrote

Dr Mitchell said there was only one way in which the breeding of a man suitable for such a position, in such a city as Philadelphia, could be tested. Give him cherry-pie and see how he disposed of the stones. I had read of the trick before, and disposed of them genteelly in my spoon—and got the Chair.

Osler arrived in Philadelphia on Oct. 11, 1884. He stayed for some days at the Aldine Hotel (since torn down) and then moved into lodgings at 131 South Fifteenth Street, a home which was later torn down (the Union League Club extended its building over the site). He was welcomed in the heartiest manner by the leading members of the profession. Cushing lists a formidable number of dinners to which he was invited. He was soon elected to the Ritten-

house Club and the University Club and to three of the dining clubs which formed so pleasant a feature of professional life in Philadelphia the Mahogany Tree, which was composed of men well known for their achievements in various activities—literary men, such as Owen Wister, and scientists, like Joseph Leidy—the Biological Club, to which Dr Leidy also belonged, and whose members were chiefly physicians and biologists, and the Medical Club, whose membership was entirely composed of physicians. The first two of these clubs no longer exist, but the Medical Club still flourishes. Osler was a constant attendant at the dinners.

His position as professor of clinical medicine carried with it supervision, with Dr Pepper, of two wards in the Hospital of the University of Pennsylvania. This stood in close proximity to the Philadelphia General Hospital, then more commonly termed "Blockley." It was the city hospital, an outgrowth of what was originally called the Alms-house, or Bettering House, as which it was established in 1731, the term "hospital" was not officially applied to it until 1824. Osler spent many hours working with his classes in the rich fields for study afforded by its wards and "deadhouse."

Osler was elected a fellow of the College of Physicians of Philadelphia in January 1885, and a year later he was elected a member of the library committee, having as fellow members S. Weir Mitchell, Minis Hays and Frederick P. Henry, who was honorary librarian. Osler was regularly reelected to the committee every year until he left Philadelphia, and he took a lively interest in the library of the College until the end of his life. From both Baltimore and Oxford, he often sent books or contributions for their purchase for the Library, and, in his last illness, he wrote a note bequeathing to the College his manuscript copy of Bernard de Gordon's "*Lilium Medicinae*," written in 1348. Dr John H. Musser was in London in 1910, and Osler arranged for John S. Sargent to draw a portrait of him in black and white, this he sent, with a companion portrait of himself by the same artist, to the College, where they were hung side by side.

In 1887 Osler was elected a member of the staff of the Orthopedic Hospital and Infirmary for Nervous Diseases, a small, special hospital with a splendid staff, including S. Weir Mitchell, Wharton Sinkler, W. W. Keen, George E. de Schweinitz and other distinguished physicians. Osler was especially interested in chorea, and he published several papers on the subject, and on cerebral palsies in children, based on studies in the Orthopedic Hospital. In the same year, Osler rented a house in which his old friend Dr Alfred Stille had lived, on Walnut Street above Fifteenth Street, and he lived there until he went to Baltimore.

A great international "Congress of Physicians and Surgeons," held in Washington in 1888, was attended by many distinguished practitioners from abroad, as well as by leaders of the profession in America. John S. Billings, president of the congress, at that time was very active in organizing the medical school and hospital to be opened at Johns Hopkins. The frequency with which Billings was seen in company with Osler aroused in the minds of some Philadelphians the suspicion that Billings was seeking to lure Osler to the new school and that Philadelphia might lose him. At any rate, in September 1888 the board of trustees of Johns Hopkins elected Osler chief physician to the hospital and he accepted. On May 1, 1889, he delivered a valedictory address to the Pennsylvania students and was given a complimentary dinner, presided over by Dr. Pepper and attended by many guests from other cities, besides a large number of the leaders of the profession in Philadelphia. Among the visitors was H. P. Bowditch, of Boston, who wrote to his family a letter (quoted by Cushing) in which he said "Osler's dinner was quite a festival. It is extraordinary what a hold he has on the profession in Philadelphia. He is one of the most popular men I ever knew."

Though Osler had hosts of friends, his closest during his years in Philadelphia were probably Dr. Gross and his wife. Gross died on April 16, 1889, and on May 15, 1892, Osler married "the widow Gross," as he used frequently to term her. Cushing¹ recalls Dr. James C. Wilson's amusing anecdote of the wedding day. In the morning Osler called at the house of Mrs. Gross. Wilson also called on the lady and was asked by Osler to stay to lunch; Wilson accepted the invitation. After lunch Mrs. Gross excused herself, stating that a hansom was waiting for her. Osler said that he would go with her if she would give him a lift. Wilson said goodby, little suspecting that his two friends had driven off to St. James's Church, where they were duly married at 2.30 p.m. Wilson's eyes were opened when he received a telegram from the happy bridegroom, saying, "It was awfully kind of you to come to the wedding breakfast." The marriage proved a great success. In Baltimore, and later in Oxford, the Oslers extended the most abundant hospitality to their hosts of friends, and Mrs. Osler's charm and loveliness won the hearts of Osler's innumerable friends. Before their son, Revere, was killed in Belgium during World War I, a more ideal home could not be imagined.

Osler always retained fond memories of his sojourn in Philadelphia. He was thoroughly familiar with its glorious past in medicine. Cushing relates how Osler once sent a recent McGill graduate, named Hewetson, who had joined his staff at Johns Hopkins, up to Philadelphia to look up something in the library of the College of Physicians, bidding him,

as he left Baltimore, "Do drop in on my old friends Philip Syng Physick, and Shippen, and give them my love" Poor Hewetson could not have been expected to know anything about these two figures of the past, and, after spending most of an afternoon trying to look them up, he returned to Baltimore, where the cause of his failure was explained to him

Among the many interesting memoirs which were published by Osler in "An Alabama Student, and Other Biographical Essays"² is one concerning Stille, who had died in 1902, aged 87 During his sojourn in Philadelphia, Osler had frequently visited the old gentleman Dr Stillé had studied under Louis in Paris, and on his return to Philadelphia had the opportunity, in 1835, to study many cases of typhoid in the wards of the Pennsylvania Hospital under Dr William Gerhard In the following year there was an epidemic of typhus and young Stille, working again under Gerhard, had the opportunity of studying the disease in the wards of the Philadelphia Hospital It was the famous studies of these cases that Gerhard published, confirming the differential diagnosis which Louis had stated existed between the two diseases

An unfortunate misinterpretation of a few statements in Cushing's great biography has given rise to an entirely erroneous view of Osler's relations with Dr William Pepper Cushing states that "Pepper's was not his [Osler's] method," and tells how Pepper on occasion, in showing a clinic patient whom he knew to have Addison's disease, lectured to the students as though the condition were jaundice Cushing adds "The two men in fact were the antipodes of each other, and a community in which Pepper held sway could not possibly hold Osler long" There was no microscope in use in the University Hospital until shortly after Osler's arrival, when he and Dr John H Musser put up \$50 each to equip a small clinical laboratory Cushing indicates that Dr Fussell was the only person at the hospital who had been taught to make microscopic examinations of sputum, and states "In all this Pepper had very little interest, though he would occasionally send a specimen to the laboratory before one of his clinics, so that he might mention the findings"

Osler's own memoir of William Pepper can be read in "An Alabama Student", it shows in what real esteem he held Pepper, and what he thought of him as a pathologist, as well as a clinician After Pepper had served his term as a resident physician in the Pennsylvania Hospital, he was appointed pathologist to the hospital and curator of its museum, and three years later, in 1868, he was appointed lecturer on pathology in the University of Pennsylvania Osler said, "Quite

² Osler, W. *An Alabama Student, and Other Biographical Essays*, New York, Oxford University Press, 1908

early in my association with him I saw that he had served an apprenticeship in the deadhouse, and he recalled that in 1869 Pepper was associated with Dr Thomas G Morton in drawing up and publishing a descriptive catalogue of the Pathological Museum of the Pennsylvania Hospital and was a very active member of the Philadelphia Pathological Society. Some years later, he founded the Pepper Clinical Laboratory at the University Hospital, in memory of his father. Pepper was one of the earliest and most active workers in the movement to elevate the standards of medical education. He established the Archeological Museum at the university, the Philadelphia Commercial Museum and the magnificent Free Library of Philadelphia. Osler concluded the tribute with a beautiful eulogy of Pepper's personal qualities.

Dr O H Perry Pepper, younger son of Dr Pepper, and later his successor in the professorship of medicine at the University of Pennsylvania, wrote a report which was published in December 1907. Some months after its publication, young Dr Pepper received a note

Dear Perry. Delighted to see your name—and associated with such a good bit of work. Send me a reprint. It is nice to see the name kept up so worthily in the third generation. My sincere regards to your mother & to Will. Sincerely yours, Wm Osler.

Enclosed with the letter was a short review of Perry's article, written by Osler himself, from the *Lancet* of April 25, 1908. The letter was typical of those which Dr Osler sent from Oxford to many of the young men who had worked with him in Philadelphia or Baltimore. Among many Philadelphians who received similar notes commending their work were Drs H R M Landis and George W Norris.

My personal relations with Dr Osler began in 1893, one year after I had graduated from the University of Pennsylvania School of Medicine. I had applied for a residency at the Pennsylvania Hospital, but at that time there were only four residents, one being elected every three months, and, though my father and brother were both on the staff, there were several applicants who, it was evident, would be elected before me. I would therefore have to wait a year before I could be elected. Dr Osler in some way heard of my plight and wrote to my brother Fred, his former resident, kindly suggesting that I come down to Baltimore, where, he said, he would give me plenty to do, though he could not offer me any position on his staff. Of course I accepted and went at once to Baltimore, where I worked in the pathologic laboratory and saw the ward work of Osler and others of the staff. It was a wonderful experience, and one which ended for me in a situation of great embarrassment. One morning Osler's

Negro servant brought me a note from the Chief, as he was generally known, in which he stated that one of the residents on his staff was obliged to leave on account of ill health, and that he would appoint me in his place. Of course I accepted with gratitude, sending a note to him by his man. Although I spent the entire day at the hospital, I did not see Osler. On returning to my boardinghouse, I found a telegram from President Shoemaker of the board of managers of the Pennsylvania Hospital. One of their residents was resigning because of illness, if I would fill out his uncompleted term the board would elect me to a full term residency. In another telegram, my father urged me to accept Mr. Shoemaker's offer. With much trepidation, I took my telegrams and went down to Osler's. There was a mischievous twinkle in his eye as I explained the situation. He asked me where I expected to practice, to which I replied, "In Philadelphia." He spoke of the connections of my great-uncle, George B. Wood, and my father and my brother with the Pennsylvania Hospital and expatiated on its fame. He mentioned Rush, Physick and other great men who had served it and then suddenly bade me take a train to Philadelphia as soon as I could. I took his advice.

Another episode illustrates his great kindness and his affection for those who had worked with him. My brother, Frederick A. Packard, had graduated in medicine at the University of Pennsylvania in 1885 and had then been appointed a resident at the University hospital. I can recall the enthusiasm he expressed when on Osler's service, later, he modeled his own practice and teaching at the Pennsylvania Hospital on that of Osler, until his own untimely death in 1902. Osler, in return, appreciated Fred's ability and character. Cushing quotes from a letter of Osler's, written to John H. Musser and dated Jan. 10, 1889: "I have with P's [Pepper's] consent appointed Fred Packard." Fred declined the flattering proposal, as his prospects were bright in Philadelphia, but he always looked back on it with pride and pleasure. In October 1902 my brother was desperately ill with typhoid, in the Pennsylvania Hospital. Osler telephoned me and asked whether he could come up from Baltimore and see him. I, of course, replied in the affirmative, we fixed a time, and at Osler's suggestion I told my brother's physician that Dr. Osler expected to be in Philadelphia and had asked if he could see his ex-resident. He readily assented and said that he would meet him at the hospital. What it meant to Fred I cannot attempt to describe. An ulcer had perforated his intestinal wall, he had been operated on and we all felt that he had no chance, but Osler bucked up not only the patient but also the physicians and surgeons. Everything went better for a few days, until my brother's death on November 2.

During World War I, I was detached from my unit and worked temporarily in a clearing station beyond Poperinghe, in Belgium. On Aug. 30, 1917, I heard that Osler's son had been brought into the clearing station next to the one where Dr. Charles F. Mitchell and I were one of the teams. We walked right over to the next station, where the poor boy had just died of terrible shell wounds. We accompanied his body out to a trench in which a number of soldiers were being buried. It is curious how many of Sir William's ex-students or assistants were present at the funeral. Harvey Cushing, Brewster, St. John and Woolsey, of New York, and Mitchell and I, from Philadelphia, were all working in neighboring clearing stations and had hastened to pay our last respects to the son of our beloved teacher and friend.

304 South Nineteenth Street

ADDITIONAL NOTES ON OSLER IN PHILADELPHIA

EDWARD B KRUMBHAAR, M D
PHILADELPHIA

BY THE year 1884, when William Osler had completed exactly one-half his life span of 70 years, the lines of his medical development had become established. His philosophic viewpoints, his special interests, his systematic habits of work, his ability to think constructively and penetratingly, and to set forth the results in an arresting style, were already bringing him a well deserved reputation on both sides of the Atlantic. It is not surprising, then, that when the chair of clinical medicine at the University of Pennsylvania was vacated by the promotion of William Pepper to the professorship of medicine, Osler should have been chosen as his successor.

The circumstances of his selection were about as follows. A name had been proposed by the faculty to the board of trustees after what seemed to some an insufficient consideration of the subject. According to Minis Hays, the matter came up in a conversation at a meeting of the editors of the *Medical News*, and Osler's name was suggested. Tyson, the only member of the University faculty at this meeting, and later to be Osler's successor, discussed the subject with H. C. Wood, the only member of the faculty available at the moment. Wood, with characteristic energy, skipped off to Montreal to get firsthand evidence and returned "a thorough convert." Many years later (1905) Osler spoke of S. W. Gross and Minis Hays as responsible for his selection. Tyson then wrote to Osler, who was in Leipzig, and was told that he would be a candidate. Weir Mitchell, who was also in Europe, was commissioned to look over Osler, with power to act, and sent for him to come to London. It was there that the cherry stone test of breeding was applied. Osler, speaking in 1905, said "I had read of the trick before, and disposed of them genteelly in my spoon—and got the chair." One wonders how much poetic license should be ascribed to this tale, like the one told by him even later to the American Rhodes Scholars at Oxford (1916), that his decision to go to Philadelphia was based on the toss of a coin.

From the Department of Pathology, University of Pennsylvania School of Medicine

To Cushing,¹ Osler's reasons for accepting the Philadelphia offer were not clear. Osler himself, in a letter to H. V. Ogden, wrote of the temptations of the larger center and the prospects of consulting work, though he was never avid for even this kind of private practice. The greater opportunities for developing a new type of clinical instruction and for advancing his own medical knowledge would seem to be a sufficient explanation, just as, when such opportunities seemed still greater in Baltimore, four years later, Osler promptly moved again. The action of the university—then "the Premier School in America," as Osler later called it—in appointing to an important position a young man "from out of town," with extremely unconventional ideas about medical teaching and practice, must have been a shocking surprise to conventional Philadelphia. It was a significant step forward in the reform of medical education in this country, one which had been begun by President Eliot at Harvard in 1870 and continued by Stillé and Pepper a few years later in Philadelphia.

Osler entered unobtrusively into his new job at the University Hospital. The problem of selecting Pepper's successor had aroused considerable feeling in the faculty, but it is illuminating that, as H. A. Hare put it, his "plunge into the pond at once had the effect of making the surface placid." There, as later at Baltimore and Oxford, Osler's pervasive enthusiasm and his imperturbable friendliness, agreeably punctuated with his mischievous whimsies, soon won him the affection of his colleagues and the respect of the Philadelphia profession at large.

At the hospital, Osler shared the medical wards with William Pepper, who had founded the institution only a few years before. His arrival there must have surprised students and staff alike. As Cushing¹ describes it:

No polished declamations with glowing word-pictures of disease came from this swarthy person with drooping moustache and informal ways, who instead of arriving in his carriage, jumped off from a street-car, carrying a small black satchel containing his lunch, and with a bundle of books and papers under his arm, who was apt to pop in by the back door instead of by the main entrance, who, far from having the eloquence of his predecessor, was distinctly halting in speech, who always insisted on having actual examples of the disease to illustrate his weekly discourse on Fridays at eleven, and, as likely as not, sat on the edge of the table swinging his feet and twisting his ear.

Pepper, then at the height of his amazing career, provost of the university, with a large practice and busily engaged with plans for his city and university welfare, had but little time left for work in the wards. There Osler was at his best, in his favorite kind of teaching, as students were quick to appreciate. The medical dispensary (out-

¹ Cushing, H. *The Life of Sir William Osler*, Oxford, Clarendon Press, 1926.

patient department) was also quick to feel his influence, its well studied cases serving with those in the wards as material for his investigations and conferences. At the conferences, correlation of other factors with pathologic anatomy was emphasized, the organs in the fatal cases being demonstrated by Osler himself, the method has now long been commonplace but was a distinct clinical innovation at that time. His own Zeiss reenforced the decrepit microscope without oil immersion lens that graced the outpatient laboratory, and soon after his arrival a clinical laboratory appeared beneath the hospital amphitheater. The ward exercises, which had been introduced a few years before Osler's arrival and at which, on rare occasions, the student had an opportunity to percuss and auscultate, were enthusiastically supported and expanded by him to include more individual student-patient contacts.

One would like to know how Osler conducted his examinations in those days. The only clue that I have found is a signed page in Osler's writing on marks in the course on clinical medicine in 1885. Based on a maximum of 400, the marks ranged from 286 to 383, i. e., percentages of 71 to 95, not unlike those a section might be given today. The ten names included those of Gregorio Guiteras, Allyn, H. C. Deaver and Fred Packard. If conducted orally, the examination must indeed have been entertaining.

Before long, other hospital appointments added to Osler's opportunities for medical studies. Especially at nearby "Blockley" (by then officially the Philadelphia Hospital), he rejoiced in the abundant clinical and pathologic material. Long hours in the wards, usually surrounded by interns and students, were often followed by autopsies, performed by him in cases not limited to those in his own service. The program might begin at 8 a. m. and go on until evening, while Osler hunted perhaps hours for the ruptured artery in a case of pulmonary hemorrhage or hemiplegia. The old "deadhouse," which still contains the autopsy table at which Osler worked, is now the Osler Memorial Building. In it may be seen the huge autopsy books, showing that from 1885 to 1889 he performed 162 autopsies, the record being either dictated to an intern or, more often, written up in his own hand. Now and then, when subsequent study showed that a statement should be modified, marginal notes appear. "A small cavity *was* found later at the right apex." The Pathological Museum, until its recent dispersal still contained a few specimens from the autopsies he had performed.

In a letter to Dr. J. W. Croskey, who was writing "A History of Blockley,"² Osler said: "I look back with rare pleasure to my term of service. My appointment I owe to Dr. Pepper. The wards were always full of interesting cases and my literary output, while in

² Croskey, J. W. History of Blockley. A History of Philadelphia General Hospital from Its Inception, Philadelphia, F. A. Davis Company, 1929.

Philadelphia, came very largely from the Philadelphia Hospital service. The malaria service was of special value " 3

At the Philadelphia Orthopedic Hospital and Infirmary for Nervous Diseases (now merged with the University Hospital), Osler found rich neurologic material. Elected to the staff in 1887, he shared the ward and outpatient clinics with Weir Mitchell and Wharton Sinkler and, among the juniors, with Burr, Dercum and Morris Lewis. One of his best likenesses is in a photograph of a group at "the Infirmary," including de Schweinitz, J. K. Mitchell, three trained nurses and two small patients. His attractive features, with their combination of mature self confidence and a characteristic whimsical expression, are in my opinion nowhere better depicted.

Osler's interest centered especially on chorea. A study of 410 cases resulted in a valuable article,⁴ and in "The Cardiac Relations of Chorea,"⁵ he emphasized the extraordinary frequency of mitral valvulitis, which often "lays the foundation of organic heart disease." In this article one finds, italicized for emphasis, the statement: "*There is no known disease in which endocarditis is so constantly found, post mortem, as chorea*" His other important study there, "The Cerebral Palsies of Children,"⁶ begun as five clinical lectures at the Infirmary, was published in the *Medical News* and later expanded into a book of 111 pages. At the Orthopedic Hospital, too, he observed the family described in his oft cited article on "Hereditary Angio-Neurotic Oedema."⁷ Infirmary material was also responsible for his report of a case of idiopathic muscular atrophy⁸ and for one on sensory aphasia,⁹ though the latter was published after his move to Baltimore.

Osler's concern with the role of medical societies in professional life—already manifest in Montreal—had full scope in several of the Philadelphia societies. His interest was shown not only by regular attendance, which he recognized as an obligation and discharged as

3 The remainder of the letter is quoted by Cushing,¹ in vol. 1, p. 290.

4 Osler, W. On the General Etiology and Symptoms of Chorea, Based on the Records of Four Hundred and Ten Cases at the Infirmary for Nervous Diseases, *M. News* 51:437, 465, 1887.

5 Osler, W. The Cardiac Relations of Chorea, *Am. J. M. Sc.* 94:371, 1887.

6 Osler, W. The Cerebral Palsies of Children, Philadelphia, P. Blakiston's Son & Co., 1889, *M. News* 53:29, 57, 85, 113 and 141, 1888.

7 Osler, W. Hereditary Angio-Neurotic Oedema, *Am. J. M. Sc.* 95:362, 1888.

8 Osler, W. On a Case of Simple Idiopathic Muscular Atrophy Involving the Face and the Scapulo-Humeral Muscles, *Am. J. M. Sc.* 98:261, 1889.

9 Osler, W. A Case of Sensory Aphasia. Word-Blindness with Hemianopsia, *Am. J. M. Sc.* 101:219, 1891.

a pleasure, but also by frequent discussions on the floor and in the corridors, by suitable contributions and even by active promotion of new organizations when they seemed to him necessary. For instance, he was a founder of the Association of American Physicians, having been one of the organizing group of six that met in October 1885, after having exerted his catalyzing powers toward that end since 1881. He was one of a committee of three to draw up the plan of organization. At the opening meeting the following June, "the coming-of-age party of internal medicine in America," as Osler put it, he contributed a brief paper on 18 cases of bicuspid aortic valves.

The Pathological Society saw him most. The second oldest society of its kind still in existence, it was at that time in its twenty-eighth year, a flourishing body of 162 members with well attended semi-monthly meetings. The study of morbid anatomy was still to be for some years the royal road to clinical supremacy, though few will agree with Cushing, who wrote in the twenties¹⁰ that it "always has been and always will be the only way to reach the very top either for surgeon or physician." Osler, fortified by his nine years' pathologic experience at Montreal, from the start took an important part in the society's meetings. His first presentation, a report of a case of ruptured aortic aneurysm, was made within a month of his election, on March 12, 1885, in it, he characteristically devoted more space to the clinical than to the postmortem picture. In the "Indexes of Proceedings" for the ensuing four years, 53 contributions by him are listed. Among the subjects are the study of the hematozoa of malaria, tuberculosis of the lungs and adrenals with symptoms of Addison's disease, aneurysms of the larger cerebral arteries (12 cases, 2 probably congenital) and a rupture of a papillary muscle of a normal mitral valve ("unique in my experience"). During most of his Philadelphia stay, Osler was on the society's committee on morbid growths, and for some time after he moved to Baltimore he continued as a nonresident member of the society.

Osler was an active contributing member of the newly created (1884) Neurological Society throughout his stay in Philadelphia, "Blockley" and "the Infirmary" producing most of his neurologic material. Dr C. K. Mills speaks of his being particularly happy and at home there with a group that included Weir Mitchell, Wood and Dercum.

The College of Physicians of Philadelphia—a collegium in the ancient sense of a group of persons united in the same calling—elected him to fellowship at the earliest possible moment, in January 1885, a few months after his arrival. One can be sure that he attended the meetings regularly and took an active part in the general programs

¹⁰ Cushing¹ vol 1 p 147

which were then the order of the day. Exactly a year later he was made a member of the library committee, the splendid library being then, as now, one of the chief assets of the college. In its reading room and stacks he was in his element, prowling among its historical treasures and keeping abreast of current progress—charting the sea on which his clinical ship was sailing, to paraphrase his dictum on the place of books in medicine. Osler's interest in the library of the college continued throughout his life. In the memorial volume by Maude Abbott,¹¹ there is a list of 54 items presented by him to the college library, sent mostly from Baltimore and Oxford. How many more he was instrumental in having bought will never be known. Several times a year would come brief letters of congratulation on a worthy acquisition, or a note suggesting that he give some rarity he had seen or picked up. These form the bulk of the 84 notes from his pen in the college archives, many saved by his good friend, Charles Fisher, the librarian. In one such note, written in 1891, he concludes, "I miss the Library very much. For it alone it would be worth returning to Philadelphia." Characteristic was a note in 1913, accompanying a book by Synphorien Champier: "Champier was a great old character and all his books are worth buying. It would be nice if the College could issue a small separate catalogue of the incunabula", the catalysis soon produced the desired effect. His last gift, made on his deathbed, was "that Montpellier MS," a valuable text of 1373 by Bernard de Gordon. Two further instances of his continued interest. When subscriptions for the new building of the college were being sought, about 1908, a handsome check arrived from "Dr and Mrs William Osler", his nonresident fellowship was continued until his death.

Osler's most important scientific work while in Philadelphia was on malaria, on which he had plenty of material in the hospital wards. It was characteristic of the man that when Councilman reported at the opening meeting of the Association of American Physicians on the organisms found in malarial blood, first described by Laveran a few years earlier, Osler was skeptical that the bodies represented organisms. However, he was led to spend the ensuing hot summer in Philadelphia, resisting the temptations of "cool Toronto," to such good effect that by the end of October he was able to report ample confirmation, based on 52 cases, in the Conversational Lecture of the Philadelphia Pathological Society. To him has also been given the credit for

11 Abbott, M. Sir William Osler Memorial Number. Appreciations and Reminiscences, Bulletin 9, International Association of Medical Museums. Toronto, Murray Printing Co., Limited, 1926.

demonstrating that identification of the malarial organism could be used in practice for diagnosis

Besides Osler's major articles, there was a constant stream of literary output, in such forms as the editorials in the *Medical News* (well over 100 in number, and mostly unsigned), the "Notes and Comments" in the *Canadian Medical and Surgical Journal*, book reviews, 30 odd presentations at the Pathological and Neurological Societies, obituary remarks and signed correspondence. From April 1886, when he took charge of the medical section of *Progress of Medical Sciences* of the *American Journal of the Medical Sciences*, abstracts appeared on a wide range of subjects, some, without doubt, having been prepared by assistants

Some idea of Osler's productivity during his Philadelphia sojourn may be had by comparing, in Abbott's classified bibliography,¹² the number of pages given to Osler's written output in three of the major periods of his life. Actually, more space is required to list the work of the four years of the Philadelphia period than for that of either the sixteen years in Baltimore or the fifteen years at Oxford. No wonder he spoke of it as the most productive period of his professional life! "Both pen and brain got a deal of practice in Philadelphia," as he later wrote. Nor is it surprising that this should have been the case for an energetic man in his thirties, with a well planned way of life, surrounded by opportunity and unencumbered by the entanglements which even he eventually could not altogether avoid.

To his Philadelphia contemporaries, as well as in the factual record, Osler had already shown the teaching qualities which distinguished him from the rather florid habits of the period. To one who first got to know him much later, his outstanding trait was his quiet and thorough study of the patient, both by the time-honored methods and by the few clinical laboratory methods then available. His teaching was always directly from the patient, his comments in conferences and in the wards being limited to his own observations and to what had actually been demonstrated, to the exclusion of hypotheses and mere tradition.

His writings and public addresses were to the point and well carried out, but even at that time rather full of often farfetched allusions. As J. C. Wilson points out, in the eighties these were more from the Bible and "Pilgrim's Progress" than from his later favorites, Montaigne, "Religio Medici," Plato and Marcus Aurelius. Even at that early period, Osler was regarded as a therapeutic nihilist, but that was because so few reliable drugs were known at that time. His rational use of

¹² Abbott, M. Classified and Annotated Bibliography of Sir William Osler's Publications (Based on the Chronological Bibliography by Minnie Wright Blogg), ed. 2, Montreal, The Medical Museum, McGill University, 1939.

drugs was merely in advance of his time, while his general management of a case was well and carefully attended to. He was feeling his way, conducting surveys on comparative methods of the treatments of pneumonia and typhoid, studying the effects of arsenic, iron, digitalis and a few other drugs and, *faute de mieux*, using harmless placebos, together with "time in divided doses" or "hope and nux vomica."

Soon after Osler's arrival in Philadelphia, on Oct 11, 1884, his social contacts began to expand. Weir Mitchell, J. C. Wilson, James Tyson, H. C. Wood, S. W. Gross, Wharton Sinkler, F. P. Henry and Minis Hays were among his best friends. J. C. Wilson lived but a few doors from Osler's apartments at 151 South Fifteenth Street (later to make way for the addition to the Union League Club). The younger Dr. Gross and his wife also lived nearby, at 1112 Walnut Street, he came to visit their home with increasing frequency for a Sunday meal or for afternoon tea, a refreshment sorely missed by the expatriated Britisher. Here was founded the friendship that continued until Gross's death in 1889 and led to Osler's marriage to his widow, Grace Revere, in 1892. The Rittenhouse Club and the University Club, only a block away from his rooms, were used by Osler more for the seclusion of their comfortable, well stocked libraries than for the more customary purposes. His nonprofessional social needs were easily satisfied in the houses of his friends and in several social dining clubs. These were the Biological Club, which afforded contacts with the celebrated Joseph Leidy but did not survive the latter's death, in 1891, the Mahogany Tree, now also long defunct, and the Medical Club ("The Club of 19"), which still exists. More of a busman's holiday was the Journal Club, which in Philadelphia, as was the case with its counterparts in Montreal and Baltimore, Osler was instrumental in founding as a means of keeping the members informed of the latest medical developments. Emphasis has often and properly been laid on the importance of Osler's personality and his individualistic teaching method in making him the greatest clinician of his day. Such figures, unfortunately, tend to be the more rapidly blurred in historical perspective by the enveloping mists of time. Let us hope that the name of William Osler will never be excluded from the list of the master clinicians of our age.

Most of the factual material in this article may be found in Harvey Cushing's "Life of Sir William Osler,"¹ in Maude Abbott's volume, "Appreciations and Reminiscences,"¹¹ and in her "Classified and Annotated Bibliography of Sir William Osler."¹²

THE JOCULAR SIDE OF OSLER

GEORGE BLUMER, M D

SAN MARINO, CALIF

Give me a sense of humor, Lord,
Give me the grace to see a joke,
To get some happiness from life,
And pass it on to other folk

—From an old prayer found in Chester Cathedral

STEPHEN LEACOCK, who could obviously qualify as an authority on the sense of humor, stated as a prime quality of that saving grace that it must be without harm or malice. No one who knew William Osler would claim that his strong appreciation of the jocose was of the satirical or barbed variety, rather was it warm and kindly. There are, and probably always have been, those who regard jocularities as beneath the dignity of great men, but I suspect that such people have confused dignity with pomposity, and that many of their exemplars were not great men, but merely stuffed shirts. I have known many men, of varying degrees of distinction, but I have never known a really great one devoid of a sense of humor. On the other hand, most narrow and bigoted reformers are sadly lacking in that quality.

A sense of humor is a thing of the spirit and, like other such attributes, is not confined to written or verbal expression. It is reflected in the way of life of the person who possesses it, and I cannot but feel that in William Osler it was responsible, at least to some extent, for the affectionate regard of his patients, and, from the psychologic standpoint, for part of his success in handling them. There was nothing of what some caustic critic of modern medicine has called "the assembly line technic" in the way in which the Chief managed his patients. He was particularly fond of children and his favorite remark on greeting a new young patient was "Well! Are you feeling nice and fat today?" This, with the genial and friendly tone in which it was uttered, usually put the young patient at ease and at once established cordial relations. With adults, too, Osler often began the interview in a humorous vein and, I have no doubt, both pleased and astonished many patients who, in view of his countrywide reputation for professional eminence, had expected to meet a solemn, and perhaps austere, person. But Osler possessed not only extensive knowledge but also great wisdom, and no one knew better than he that the physician who can, from the beginning,

establish friendly relations with his patients is much more likely to succeed than the practitioner, perhaps equally learned, with a less engaging, or even a disagreeable, personality

Osler, more than any other of the "Big Four" of the early days of Johns Hopkins, developed close personal contact with his house staff and students. The latchstring always hung out at his home on Franklin Street at the traditional hour for that ancient British institution afternoon tea, and after the Medical School was founded, in the fall of 1893, groups of medical students on duty in his wards were invited over to his home on Saturday evenings to partake of refreshments, to discuss the interesting cases of the week and to listen to enlightening and stimulating talks by the Chief on some subject of contemporary interest, or on some medical worthy, whose works were often exhibited from Osler's own library. Sometimes members of his staff were regaled by jokes at his afternoon teas. One friend and former staff member tells of one late afternoon when the Chief, apparently in a state of suppressed excitement, came in and announced that, just as he had predicted, coeducation in the Medical School had turned out to be a complete failure. One third of the first class, said he, were engaged to be married. As the story got around later, it was to the effect that another third had left the school and become Christian scientists and that only one third remained as candidates for the degree of Doctor of Medicine. As a matter of fact, there were only three women in the first class, of whom one did marry a professor, one left, and perhaps did embrace Christian science, and one, who later practiced for years in Rhode Island, graduated.

Osler's jokes may be divided into major and minor ones, and the former I shall discuss in detail later. I remember one minor incident that occurred when I was on his staff. He had been called away to a distant city for a consultation and had told W. S. Thayer, then resident in medicine, that he would telegraph him the time of his return. When the telegram arrived, it was signed, "William Oyster." It is rumored, too, though I have no firsthand knowledge of this practice, that he used to tease guests at his house by making up apple pie beds in their rooms. It is quite possible that the rumor is true, as there was an element of the impish in Osler's makeup.

I remember, too, an incident which illustrated his fancy for the bizarre and unusual when there was some humorous aspect to a situation. Wishing to make a note one morning, I wandered into the main library at Hopkins to see if I could find a scrap of paper. There was a large table in the center of the room which contained a drawer, among the contents, I discovered a large, unsealed manila envelope, which I opened. I do not remember whether or not the outside was marked in any distinctive way but what I found there was a series of affidavits signed by the conductor and brakeman of a Canadian railway train, relating to

the birth of a baby These so intrigued me that I read them There was evidence that they had been collected by William Osler A young woman, far advanced in pregnancy, had boarded the train, she had gone into labor, and feeling a desire to move her bowels, she had gone to the toilet room In those days, at least on ordinary trains, the toilet was simply an open metal tube, crowned with a toilet seat The young woman, while seated thereon, had given birth to her child, who fell through the hole to the track below The mother attracted the attention of the train crew, the train was stopped and the baby was rescued unharmed, though one suspects that a few cinders may have been embedded in the region of the nates, as the child obviously had not landed on its head The incident evidently tickled Osler's sense of humor and he had collected the documents There is, of course, nothing inherently improbable about the occurrence, as anyone who reads the current news can readily appreciate Nowadays, it is so common for women to be delivered in cars, ambulances, and taxicabs as to excite hardly any comment, except, perhaps, a brief note in a local paper In the nineteenth century most women had their babies at home, and events such as the one related were much rarer

As a matter of fact, Osler actually published a report of the case, which was entirely authentic, in the *Canada Medical and Surgical Journal*¹ The mother and child had been put off the train at the nearest town, where the local physician delivered the placenta Osler not only saw the patient and the baby but examined the opening in the toilet and talked with the physician who delivered the placenta However, George Gould, knowing Osler's reputation for joking, refused to publish the account in the book on medical curiosities which he published with Pyle, even though Osler signed the article with his own name It was a case of "the boy who cried, 'Wolf!'"

One of Osler's chief medical pranks, well known to his house staff in my days as an intern, was the publication of fabricated medical reports, some of them decidedly rabelaisian, under the pseudonym of Egerton Y Davis The "Y" was for Yorrick, no doubt suggested by the familiar quotation from "Hamlet" "Alas, poor Yorick! I knew him, Horatio a fellow of infinite jest, of most excellent fancy" This, indeed, might well have been a description of Osler himself in his lighter moments As is detailed by Cushing,² Osler claimed to have known old Davis, who was described as an ex-surgeon in the United States Army, living in Caughnawaga, Quebec However, he conveniently disappeared, as W W Francis points out, just at the time that Osler left Montreal for Philadelphia, and the Chief's explanation was that he had drowned in

¹ Canada M S J 16 375 and 732, 1887-1888

² Cushing, H Life of Sir William Osler, Oxford, Clarendon Press, 1926

the Lachine rapids This was too bad, for he was an amusing old cuss, even though, according to rumor, addicted at times to the cup that cheers

I shall not go into detail as to Davis' contributions to medicine, at least one of which, refuting an absurd claim that extrauterine pregnancy could be converted by the use of electricity into the intrauterine variety, was in a serious vein Reference to the material may be found in a section on "Pseudonymous Papers," added by W W Francis, librarian of the Osler Library in Montreal, to Maude E Abbott's classified "Bibliography of Sir William Osler's Publications"³ The subjects ranged from vaginismus to Peyronie's disease and in the latter instance related to an actual case, which Osler roguishly reported under the initials of his old friend J William White, the Philadelphia surgeon White, who deduced the authorship from internal evidence, published a humorous reply in the same journal

Osler was a friend and admirer of the well known pediatrician Abraham Jacobi, whom he dubbed "the lion head of the tribe of Judah" One of his minor jokes was perpetrated in connection with the dinner that was given Dr Jacobi in 1900, in commemoration of his seventieth birthday Jacobi, of course, knew that at the end of the feast he would be regaled with congratulatory speeches and realized that some sort of a reply would be called for I had heard Jacobi speak a good many times and had never thought of him as being nervous about it, but on this particular occasion he had evidently prepared his speech beforehand and tucked it into a pocket in his coattails As the guests went upstairs to dinner, Osler, who was immediately behind Jacobi, noticed the end of the manuscript protruding from Jacobi's pocket and managed to abstract it without attracting attention When Jacobi sat down at the dinner table he noticed the absence of the paper, and, it is said, his massive brow became bedewed with cold sweat Within a few minutes, long before the time for Jacobi to speak, Osler had a waiter hand the manuscript to Jacobi with the explanation that it had been picked up on the stairs by one of the guests

Osler's students were, of course, well aware of his keen sense of humor On one occasion, when it was announced that a clinic was to be devoted to a symposium on diabetes mellitus, one of the women students repaired to a florist's and supplied herself with an abundance of sweet peas Some of these were arranged in a vase and put on the speaker's table in the amphitheater, and the remainder were distributed among the class, so that when Osler entered everyone was wearing a boutonniere This visibly tickled Osler The old amphitheater was just opposite

³ Abbott, M E Bibliography of Sir William Osler's Publications, Montreal, The Medical Museum, McGill University, 1939

Halsted's operating room, and it is reported that "the Professor" came by just before the clinic and, noting the flowers, asked what was going on. He was told that Dr. Osler was going to give a special clinic on diabetes and is said to have remarked, "Indeed, but why the flowers?" Having served with Halsted for a year, I am dubious as to the authenticity of the last statement, for, though the Professor had not the bubbling, irrepressible humor of Osler, he was no fool, and he was certainly acquainted with the urinary findings in diabetes mellitus.

In his contact with adult patients, Osler often adopted a humorous approach in order, I suspect, to put strangers at ease. One of my old friends tells me of an occasion on which an estimable matron, whose husband had died leaving her with seven children, two farms and a modest pittance, was a patient of the Chief in the Johns Hopkins Hospital. He entered the ward whistling, came up to the foot of her bed and, with a twinkle in his eye, said, "Well, madam, what in the world is the matter with you?" On recovering from her astonishment at this unexpected approach, for she had probably pictured Osler as a dignified practitioner, she smiled back and replied, "Well Dr. Osler, all I can say is that I have seven children and a farm," to which the Chief replied, "God help you, Madam, you are beyond me," and walked out. However he never failed to make her a daily visit during the remainder of her stay in the hospital, part of the time each day being spent in discussing the children and the happenings on the farm. Her tales of the latter led him to christen her "the Baroness Munchausen," but I have no doubt that his intensely human interest in her case did more to build up her morale than buckets of medicine would have.

Whenever possible, the anecdotes here related were obtained firsthand from men who had actually witnessed the occurrences or heard the remarks. There is no question that some of the stories were embellished and elaborated later. I have tried to avoid the apocryphal. I wish to acknowledge my indebtedness to friends who supplied me with details, notably Thomas R. Brown, Edward P. Carter, W. W. Francis, John F. Fulton, David C. Lyman and Joseph H. Pratt.

573 Los Arboles Lane (10)

Harry Cushing
 Henry Bacon Jacobson
 Thomas B. Fletcher
 J. C. S. - Dinner
 John G. Clark
 W. W. Ricketts
 Dr. William Osler
 George Blumer
 J. M. - Thomas
 M. C. C. - C. C.
 J. C. - C. C.
 Maryland Club
 Friday, May 15 1903, at 7 30 P. M.
 H. M. - Thomas
 H. M. - Thomas
 E. J. - C. C.
 E. J. - C. C.
 "Promptness is the one quality in a physician necessary for success"
 Lovell F. Barker
 W. S. - C. C.
 A. C. - C. C.
 H. M. - Thomas
 August 1903.

Dr. George Blumer's copy of the menu of the farewell dinner given for Dr. Osler before his trip to Europe in the summer of 1903

DR OSLER'S RENAL STONES

THOMAS B FUTCHER, M D †
BALTIMORE

[This report of a brief illness of Dr Osler's was recorded by the attending physician, Thomas B Fletcher, and was found by Dr Palmer H Fletcher in his father's files]

Patient	Dr William Osler	Dec 31, 1904
Address	1 W Franklin Street	Age 55
	Condition Married	Sex Male
Diagnosis	Renal colic, gouty diathesis	Nat Canadian

Family History—Not taken

Personal History—With few exceptions has always been a healthy man No previous attacks similar to the present one

Present Illness—While reading at the Medical and Chirurgical Library an article on "Strangulation of the Bile Ducts by Round Worms," by Ebstein, patient began to have pain in the left lumbar region of back He immediately started for home, hailing a cab on the way Pain gradually became more severe and was intense by the time he reached home about 6 30 p m It was so intense that he felt faint He immediately went to bed and a hot water bag was applied to the back It seemed to relieve the pain The attack was accompanied by garrulousness Pain had practically subsided by 8 o'clock, but was followed by considerable soreness in the left lumbar region The night and morning urine were kept separate There was no macroscopic evidence of blood in either specimen

Urine—Night Specimen High color, clear, slight cloudy precipitates, acid, 1,026, no albumin, no sugar

Microscopic No casts, an occasional red blood cell seen, numerous oxalates, no uric acid crystals

No true renal calculi found in either specimen One bottle, however, contained 3 and the other 2 quartz stones gathered from the gravel walk

Impression of Case—Patient undoubtedly had an attack of renal colic probably induced by calculus

† Dr Fletcher died Feb 25, 1938

From the Department of Medicine, Johns Hopkins Hospital and Johns Hopkins University School of Medicine

THE GAY OF HEART

THOMAS S CULLEN, M D
BALTIMORE

WHY IS it that Dr Osler—as he will always be to those of us who worked with him at the Johns Hopkins Hospital—remains in our minds so vividly and everlastingly? Random memories come to me when I think of him on his birthday. Trivial and inconsequential as they are, they emphasize two of his most striking attributes—his gaiety of heart and his friendliness.

I came to live in the southern half of the third floor of the main building of the Johns Hopkins Hospital one day in January 1892. Promptly at 10 p. m. I heard a pair of boots dropped outside the door at the end of the hall, and at 7 o'clock the next morning I heard someone pitter-pattering past my room. At 7.30 the same person was standing in front of the dining-room on the ground floor, waiting for breakfast to be served. The patterer was William Osler, and that was how I first became acquainted with him. We were friends ever afterwards.

Shortly after the hospital opened, the tradition had been established of holding a meeting of the medical society on one evening of each month. There, unusual and interesting cases were described, after which they were discussed by one or more of the Big Four—Osler, Welch, Kelly and Halsted. Dr Henry Hurd, the superintendent of the hospital, recorded in detail what was said at these meetings, and in this way he began to develop the *Bulletin of the Johns Hopkins Hospital* into an excellent mirror to reflect what those associated with the institution were doing. It was he who carefully transcribed many of the most interesting and colorful sayings of Dr Osler and the others, which otherwise might have been lost.

Occasionally the clinical program gave way to meetings of the historical society, at which old and rare medical books or pamphlets were displayed. Osler, Welch and Kelly gave the younger members delightfully memorable evenings, bringing medical history alive and weaving into the pattern bits of early literature or old tales of physicians, so that we learned to realize, with proper humility, as we took our place in medicine, that we were marching along as privates in an unending procession behind great leaders.

One night, when Dr Osler was returning by train to Baltimore from Toronto, Canada, the conductor called for a physician. Dr Osler was the only one on board, he delivered a baby in the baggage car and looked after the mother and infant on a makeshift pallet there. I have often thought that he would have made a wonderful general practitioner.

That the Big Four were fond of one another was evident in their personal relations and in their correspondence. Dr Osler's sense of humor, however, was now and then to prove an embarrassment to his friends. He was capable of almost any outrage.

One day he came to the hospital and, perhaps mischievously hoping to stir up a hospital romance, went to the telephone desk and asked for the surgical operating room. When Miss Lucy Sharp, the head nurse, answered, Dr Osler said, "This is Dr Cullen speaking. Please get ready at once for an emergency operation," and hung up.

Miss Sharp was mystified. She was friendly with the staff of the gynecologic department, of which I was a member, but the surgical operating room belonged to the department of general surgery, and she knew that I had nothing to do with it. It took fully half an hour before she found out that the telephone message was no more than another oslerian hoax and that there was no patient requiring an emergency operation.

Occasionally Osler got into trouble. One morning he was making rounds in ward C, with his usual retinue of assistants and nurses, when a student nurse appeared with a heavy wooden tray, on which was a bowl of soup covered with a napkin. Dr Osler walked over and pushed the napkin down into the soup with his finger. The little nurse—who had copper-colored hair and was pretty and very earnest—stopped short, looked him squarely in the face, reddened and said, "I don't know who you are, and I don't care, but you're the meanest man I ever saw!"

Dr Osler left the ward like a dog with his tail between his legs and went home as fast as he could. He sent Mrs Osler right back to the hospital with the most contrite note of apology he could compose.

I suspect that his peculiar mixture of foolishness and thoughtfulness of others was one of the reasons he was so dearly beloved. One never knew what he might do or say, but one could be sure that it would be original, gay and graceful. Max Brodel depicted something of this trait in his famous cartoon of Osler which he drew in 1896. The likeness of Dr Osler's head is excellent. Brodel has crowned it with a subdued halo and added a minute pair of wings and baby toes.



"The Saint—Johns Hopkins Hospital," cartoon by Max Brodel (1896), and Oslei's endorsement, signed with his pseudonym of E Y D "Egerton Yorrick Davis," from a print in the possession of Dr G C Shattuck

to the body—emphasizing, I assume, the oslerian childishness, which at times was so cherubic. The outline of the Johns Hopkins Hospital is clearly visible in the background, and a cyclone, which, since he had started it, merely supports the carefree Osler, is about to hit the side of the building. In the foreground, amebas, malarial parasites, staphylococci and streptococci are retreating from the whirlwind as fast as they can, only the typhoid bacilli are undaunted. They fear neither Dr Osler nor the storm but stand firmly upright and unmoved.

For a long time before Osler saw the picture, he had been addressing envelopes to me at 'The Saint-Johns Hopkins.' When Brodel saw them, he decided to label the cartoon with the same name, and so it has been known ever since. The original drawing hangs in my office, I value it highly.

Dr Welch and Dr Osler got a great deal of fun out of devising new ways of pulling each other's legs. I remember several of their pranks, which delighted the students at the time they were perpetrated.

Dr Welch was riding one day on the back platform of the Monument Street car, on his way to the hospital from St Paul Street, with him was a group of very dignified physicians. Dr Osler was walking west on Monument Street when he saw them. With a great flourish, he took off his hat and threw Dr Welch a loud and extravagant kiss. It tickled the fancy of his companions, but Dr Welch himself blushed fiery red.

All Baltimore chuckled for months over Dr Osler's call on Dr Welch at his rooms across town. Dr Osler rang the front doorbell and asked if Dr Welch were at home, he was not. Then Dr Osler asked how Mrs Welch and the children were. The lady of the house, who claimed to be an authority on the intimate ramifications of social life in Maryland, said that Dr Welch was not married, and that he had no children. Dr Osler, as he left, looked dubious, shook his head and announced sorrowfully, "I am afraid that you are mistaken."

Dr Welch retaliated later when Dr Osler was working on his textbook. Dr Osler called on Dr Welch and found him looking over a German medical periodical. Dr Welch said, "Listen to this, Osler, it may interest you," and proceeded to read aloud a description of a rare and peculiar aneurysm. Dr Osler was much excited, "Wait a minute," he said, then he pulled out pad and pencil and began to copy every word that Dr Welch said. When the description of the case was complete, Dr Welch began to describe a second case, this, too, Dr Osler copied. Presently Dr Welch began to laugh, for he had improvised the reports on the spur of the moment, entirely for Dr Osler's edification.

It may seem odd that insignificant memories of Dr Osler, such as these, should stay fresh in my mind for so many years, and that I should venture to write about them now in memory of the hundredth anniversary of his birth. Yet I have done so deliberately, because I feel that his minor peculiarities and idiosyncrasies accounted in large measure for his charm.

I claim that what he wrote while in our midst, in beautiful English as his writings always were, does not represent his greatest accomplishment. I believe that with his way of life, his personality, his ideals, his gaiety and kindness, he welded the medical profession of Maryland, and of the entire country, so that brotherly love became its dominant note. That, in my opinion, was William Osler's finest and most enduring contribution to American medicine.

20 East Eager Street (2)

WILLIAM OSLER A PERSONAL NOTE

JAMES B HERRICK, M D

CHICAGO

BEFORE 1892, the name of William Osler meant but little to me, he was simply one of the teachers in the new medical school in Baltimore. But when, in that year, he published his textbook, "The Principles and Practice of Medicine,"¹ all was changed. After reading its 1,079 pages, I wrote a long, laudatory review, which closed with the statement that it was not extravagant praise to call it the best textbook in English on the practice of medicine. At that time I was 31. Today, at 87, I still believe my early opinion was justified. The textbook's successive editions have well deserved the blue ribbon award of merit.

It must have been about 1898 when I first met William Osler in person. For no good reason I had pictured him as of the dignified, unapproachable type, rather paunchy and burly, perhaps with mutton-chop whiskers. One day, as I was talking with John Musser Sr., the father of the late John Musser of New Orleans, in the lobby of a hotel in Washington, the real Osler breezed in, short, dapper, slender. Unceremoniously he gave Dr. Musser a poke in the ribs and said, "Here, Musser, why don't you introduce me to Herrick?" Dr. Musser very properly introduced Herrick to Osler, who within two minutes had me in one of the horse-drawn phaetons that were then—would they were now!—so plentiful in Washington. He directed the driver to go slowly to the Surgeon General's Library, where, he said, he wished to get a particular book. Before we reached our destination, he had, like an expert reporter, pumped me dry regarding medical matters in Chicago and had learned about my own affairs and my aims. He gave me two or three hints regarding nonmedical books, for he had discovered that I, as George Vincent once said of another physician, "occasionally lapsed into culture." He introduced me to the librarian and told me how, on deposit of \$10, I could have books sent to me in Chicago. A more inspiring, delightful hour I had never spent. I had fallen a victim—a willing one—to the charm of the Osler personality.

In an address delivered in 1939 at the celebration of the first fifty years of the Johns Hopkins Hospital,² I ventured to suggest that the

1 Osler, W. The Principles and Practice of Medicine, New York, D Appleton & Co., 1892.

2 Herrick, J B. The Johns Hopkins Hospital Its Past and Its Future, Bull Johns Hopkins Hosp 65 56-68, 1939.

greatest gift that institution had made to medicine was William Osler whose writings and life had left an ineffaceable impression for good on the entire English-speaking world of medicine. I was not unmindful of the service of Howard A. Kelly and W. S. Halsted, of the so-called "Big Four." Above all, I would not underestimate the value of William H. Welch, whose constructive ability was responsible for many of the important developments at the hospital, who was the balance wheel of the medical staff and a philosopher of great knowledge and broad views whose wise counsel on medical matters was often sought in places far remote from Baltimore. Without meaning to rob any one of these three of the credit which was his due I stated my belief that the influence of William Osler was as great as, perhaps even greater than, that of any other medical man in the English-speaking world in the last one hundred years. I still hold that view. Sir Humphrey Rolleston went further, saying extravagantly that at the time of his death (1919) Osler was the greatest personality in the medical world.

It is difficult to assess at its real value such an influence as he exerted, the secret escapes one. He made many valuable contributions to medical knowledge, yet is credited with no epoch-making discovery. He was an excellent diagnostician, clinician and teacher, yet some of his pupils and colleagues were regarded as his equals or his superiors in these respects. Though an effective speaker, he had no surpassing gift as an orator.

But the favored few—students, staff members and colleagues—who in the ward, the lounge or his home library, or at the meetings of societies (so many of which he started) came into close contact with him were by the magic of his unique personality, stimulated to search at the bedside, in the laboratory, the morgue and the library for the truths of medicine, both old and new. They were led, unconsciously perhaps to appreciate the meaning of culture, scholarship and character in the physician. They saw how one whose vocation was science and medicine could yet become famous as a man of letters and a lover of books. William Osler exemplified Lord Tweedsmuir's three qualities of greatness—humility, humor, humanity. Though unusually well informed he was humble before the huge mass of new knowledge, only a portion of which could be grasped by any one man. His sense of humor which made him conscious of the inconsistencies and frailties of himself and others, saved him from many a spell of deadening depression. He was humane and human. Essentially an aristocrat, he was yet democratic in his mode of life, tolerant and accepting all men as brothers. From him, his graduates and his staff there emanated an influence for good that lifted the practice of medicine over a wide area to a higher level than was before known.

The "Textbook on Medicine" was rightly termed, by Harvey Cushing, "Osler's medical masterpiece." It was a carefully edited compendium of the essentials of medicine. Bewildering theories and unproved facts were omitted, useless, or possibly harmful, therapy was condemned, unnecessary verbiage was deleted. In fine, it was practical medicine reduced to lowest terms, stated in clear, direct language, yet so shot through with the individuality and sane judgment of the author that it impressed the reader not as a mere compilation, but as a carefully prepared summary. Like a lawyer's brief, it presented the facts fully, while at the same time, like a judge's charge, it interpreted them fairly.

Furthermore, the book was a potent connecting link between the profession of medicine and the public. It is a well known fact that it had much to do in inducing laymen to contribute large sums to further medical research and to sustain efforts, in this country and elsewhere, to prevent and combat disease.

I have no desire to debate the question of the comparative merits of research and textbook authorship. If I were to attempt it, I fear I should make a poor showing in trying to prove that any textbook has benefited mankind as have the researches of a Galileo, a Harvey, a Newton, a Pasteur, a Koch or a Roentgen. But a strong case could be made for the claim that honorable mention may justly be accorded the author of a good textbook. As a supporting witness, I should call in William Raney Harper, who, many years ago, said to me that though he himself was a devotee of research and the president of a university the major activity of which was original investigation, he was unwilling to say that the contribution of one who sought for the new was of greater value than that of the competent teacher or the writer of a genuinely good textbook, who made known and interpreted the old. As I see it, such a service was rendered by the textbook of William Osler.

For several years before Dr. Osler left America for England, where he was to become Sir William Osler, we met not infrequently at sessions of the Association of American Physicians or of the American Medical Association, and occasionally at the banquet table. Our acquaintance was also kept up through correspondence. As is well known, Osler was addicted to the "brief note habit." There might be an encouraging word about a recently published article, a hint to be attentive to some former pupil of his who would soon be passing through Chicago or a hope that I would be helpful to the recently appointed professor of medicine in a western medical school. "He is a splendid fellow." There were more formal letters, which were dictated, and in which words were spelled in full, deciphering one of his postals was almost like solving a cryptogram. These contacts, whether personal or by letter, always showed his cordial, helpful spirit, his occasional quippish comments revealed a lively sense of humor. It is to be added that my experience was by

no means unique. Hundreds of other physicians were on his friendly "brief note" mailing list.

Dr Osler was not infallible as a practitioner or as a teacher. He made his share of errors in diagnosis and occasionally missed the mark as a teacher. He had, too, some traits that, if one were disposed to be hypercritical, might be said to reveal a weakness in his character. For example, he enjoyed playing practical jokes on others but was almost childish in his resentment at a joke played on himself. One day, when Dr Ludwig Hektoen and I were making a trip to visit medical schools in the East, we walked unannounced into the Johns Hopkins Hospital. On inquiry, we learned that Dr Osler and Dr Simon Flexner, the very men we wished to see, were in the morgue. When we entered, Dr Flexner had not begun the necropsy. He was waiting for Dr Osler to finish an examination, such as he often made before the pathologist took over. Dr Osler would cut through the tissues, I believe in the second left intercostal space, close to the sternum. Through the little "window," as he called it, he could see whether the heart was dilated at this point, as it would be in case certain valvular lesions were present. He was interested because the pathologic change helped to explain certain signs that were made out on percussion, and a bulging that was often seen in the roentgenogram. As he finished his little curtain raiser to the autopsy, he said, "Look at this!" It confirms my diagnosis of a mitral valve lesion. Now, the associate professor of medicine," he added jocosely, looking toward Dr Thayer, "has had the temerity to diagnose a congenital defect." "No, no," deferentially said the timid Thayer, "I merely suggested that there were some features that made me think of congenital heart disease." "Now, my dear doctor, you can't get out of it. Stand up and take it like a man, don't go back on your diagnosis."

Dr Flexner rather hurriedly examined the heart, but the valves, including the mitral valve, seemed normal. There was a moment of hesitation and perplexity. Then some one, a bright resident perhaps, said, "How about the undefended space?" Dr Flexner held the heart up, and there, in the upper part of the interventricular wall, was an opening the size of one's forefinger, unquestionably a congenital defect. As Flexner gave a quizzical look at Osler, who was silent, I turned to Dr Hektoen—he and I were sitting on the benches, with some fifteen or twenty other onlookers—and said, "Well, that's one on the old man, all right. I wonder how he'll take it." We looked, and all we could see of the Chief were his coat-tails, as he hurried out through the door. Thayer looked embarrassed, but happy. Everybody else had on a broad grin.

The next day, I spent a delightful two hours with Osler going through the hospital. We saw many interesting cases, we discussed

the method of treatment in the wards and the place of the laboratory and the dispensary in medical education. Never once did he refer to the diagnosis that he had missed. Whether he spoke to Dr. Thayer about it I never knew, but of one thing I was certain. Osler did not like it.

My acquaintance with Dr. Osler may be called intimate, though it was no more so than that of scores of other physicians in the United States, Canada and Great Britain. He had, to a rare degree, the faculty of making friends. Only once did I feel that I had been admitted to the intimacy reserved for his closer friends. At the meeting of the American Medical Association held in 1902 at Saratoga Springs, I sat next to him in the Section on Physiology and Pathology. (In those days the sections were small, often being attended by less than a hundred, discussions were more informal than they are today, when the speaker reads a carefully prepared "discussion" from a raised platform, through a microphone, to an audience of perhaps a thousand.) A paper was presented by Dr. Victor C. Vaughan of Ann Arbor, on Ehrlich's side chain theory, which was then a front page topic in high grade medical circles. Dr. Vaughan knew his subject. He drew on the blackboard the benzene ring and tacked on or took off a hydroxyl molecule here or something else there, he talked of toxins and haptophores. Dr. Osler listened intently and then, as Dr. Vaughan closed, turned to me and said, I thought seriously, wistfully and pathetically, "Herrick I wish I were 19 and had it all to do over again." Soon after, he went to Oxford. I have wondered whether one of the reasons for his leaving America at the relatively early age of 57 was not a consciousness that he could no longer keep up with the rapid advances in medicine.

I cherish the mementoes of William Osler: the brief postcards, the initialed reprints, the autographed copy of Little's "*Médecine et médecins*,"³ which he and Gideon Wells sent me from England in 1905, his cordial invitation to stop, when at Oxford, as a guest at 13 Norham Gardens. I cherish the memory of this man who was great in learning and scholarship, and whose infectious personality influenced for good all who came within its range. It was a rare privilege to know him.

70 East Cedar Street

³ Little, M. P. E. *Médecine et médecins*, Paris, Didier & Cie 1872

DR OSLER'S USE OF TIME

GEORGE DOCK, M D

ALTADENA, CALIF

“HOW DID Doctor find time?” is a question frequently asked of persons who knew Osler. Only those who have thoroughly studied Harvey Cushing's “Life”¹ can understand the fundamental reason—the thorough drilling in the preparation of life, whether that life was to be devoted to the priesthood, the practice of ophthalmology or what it turned out to be, the scholarly and investigative medical career, of which it was one of the finest examples. Learning early the master word, “work,” Osler was able to use it, often automatically, and to achieve results without apparent effort. I witnessed a striking instance, the details of which were inaccessible for more than fifty years, which is of interest in this period of reminiscence. The starting point did not escape the keen eye of Dr Cushing, who mentioned it briefly.¹

Word came from [Dr F J] Shepherd on July 31st telling of Richard MacDonnell's death—“the seed had fallen on good ground.” It was a sad business and Osler felt the loss deeply, setting himself as usual to the prompt payment of an obituary tribute to his friend of Montreal days.

According to Dr W W Francis, librarian of the Osler Library, Dr Osler answered Shepherd's telegram with a letter, written on Aug 2, 1891, from the Maryland Club. The letter, with the obituary now reprinted, was in Cushing's unabridged manuscript, but was left out, with much other material, in the printing.

My relation to the matter was incidental. Dr Osler, putting the finishing touches to the manuscript of “The Principles and Practice of Medicine,”² and living in the house officers' quarters of the Johns Hopkins Hospital, had invited me to spend the week end. I was to have the room of an intern on vacation and to take lunch with Osler and his brilliant, lovable resident physician, Dr Henri A Lafleur. Lafleur had just been appointed assistant to the chair of practical and clinical medicine at McGill, and I was going to the chair of medicine at the University of Michigan. Dr Osler had promised to give us his parting blessings, and some fatherly advice on our future work.

1 Cushing, H. Life of Sir William Osler, Oxford, Clarendon Press, 1926.

2 Osler, W. The Principles and Practice of Medicine, New York, D Appleton & Co., 1892.

At noon on Sunday, August 2, we walked to the Maryland Club, and as we entered Dr Osler was handed a telegram, which he read and passed to Lafleur. It announced the death of Dr Richard MacDonnell, Osler's former colleague and Lafleur's teacher, and obviously was a blow to both, but it did not affect Osler's imperturbability, well known to all his friends. He took us into the dining room and entertained us as though the future of us two were his sole interest. We returned to the hospital, and, as we went to our several rooms, Dr Osler asked Lafleur to lend him his copy of "In Memoriam."

In little more than two hours we met in the lobby and started again for the Maryland Club. At the first corner Dr Osler handed me a letter, as I was nearest the mailbox, and asked me to drop it in. As I did so, I noticed that it was addressed to Dr Frank Foster, editor of the *New York Medical Journal* and a close friend of Dr Osler, and that it was larger than an ordinary letter. The next day I returned to Philadelphia, where I was working in the library of the College of Physicians, and in just a week I read the obituary. Evidently Dr Foster had hastened it through the press. Recalling the loan of "In Memoriam," I looked for an extract in the obituary, not finding one, I read all of the poem, in which Tennyson mourns the early death of his friend, Arthur Henry Hallam, and found nothing applicable to the case of the young Canadian physician. I turned then to Shelley's "Adonais," the elegy on the death of John Keats, and, in canto XLV, I found the appropriate and dignified line that Osler had used. In short, on a hot Sunday afternoon Dr Osler had written an article of almost 500 words, he had rejected one source of quotations and found one he liked, and within a couple of hours he had put the manuscript in the mail. Although unsigned, the article reveals its authorship in two favorite references of Dr Osler's—the first to Oliver Wendell Holmes, the second to the touching lines from the "Trompeter von Saekkingen"

RICHARD LEA MACDONNELL

Rarely has the profession of Canada suffered a more serious loss than by the death of Dr MacDonnell, of McGill University, which took place in Montreal on the 31st ult. In him were possibilities of which the past had given full earnest, and the deepest sadness is in the thought of a life of as much promise thus prematurely removed. Although only thirty-five years old, he had reached a position which gave scope to abilities of first-class order and afforded opportunities of impressing upon a large class of students those qualities of mind so essential in the teacher, so priceless to the taught—honesty, system, and painstaking care.

Upon the death of Dr Palmer Howard, three years ago, Dr MacDonnell followed Dr George Ross in the chair of clinical medicine, a position which his father had occupied in 1845. He had previously been elected on the staff of the Montreal General Hospital. The pages of the *Montreal Medical Journal* for the past

twelve years attest the diligence with which he worked at his profession. Of late he has been a valued contributor to our columns, and only three weeks ago we published an admirable lecture of his—probably his last communication.

Four years ago Dr MacDonnell had a severe attack of inflammation of the lungs, which was thought possibly to be tuberculous, but after a winter abroad he returned in excellent health. During the past session of the school he was vigorous and well, and accomplished a large amount of literary work. Two months ago he began to fail in health, and went earlier than usual to his summer residence on the lower St. Lawrence, but pulmonary symptoms developed with great rapidity, and he died a few days after his removal to Montreal.

Very few men have entered upon the race with greater advantage than Dr MacDonnell did. To a fine physique and presence, and a charm of manner which is so often continued in this country in the second generation of Irishmen of the Brahmin class—to use an expression of Oliver Wendell Holmes's—there were added those mental gifts which alone assure success—industry and perseverance. Very early in his career circumstances in connection with the accidental death of his father altered his surroundings and threw upon him responsibilities that were faithfully and courageously met, and that gave an unmistakable stamp to a character naturally refined and noble. Success came, cares lightened, and, with domestic, social, and professional relations of the happiest possible kind, the future could not have looked brighter, but—*es hat nicht sollen sein*, and a devoted wife, an aged mother, and a loving sister, with colleagues, students, and friends, mourn his untimely union with

“The inheritors of unfulfilled renown”³

397 Calaveras Street

³ Richard Lea MacDonnell, obituary, New York M J 54 162 (Aug) 1891

DR OSLER SCIENTIST AND TEACHER

RUFUS COLE, M D
MOUNT KISCO, N Y

THE INVITATION to contribute to the Osler memorial number of the ARCHIVES OF INTERNAL MEDICINE was accepted with a little reluctance. I welcomed the opportunity to reveal my deep affection for this great man, and to express my high appreciation of his unusual qualities of mind and heart. But the invitation was accompanied with the suggestion that I name the particular characteristics of Dr Osler which in my opinion made his impact on medicine so important that after a hundred years the anniversary of his birth should still be celebrated. That requires more than a eulogy, it demands that one make a frank analysis of Osler's qualities, which to one who loved and honored him, and was ever ready to obey him, would seem almost like sacrilege, as well as being presumptuous. It would be like performing an autopsy on a dear friend. Too, one is fearful of probing too deeply, for fear of revealing unsuspected defects. One would prefer simply to accept his greatness as established.

I was associated with him during ten years at about the turn of the century, from 1896 to 1906, first as his pupil, then as an assistant and, just before he left for Oxford, as his resident physician. At one time I was also his patient, for he looked after me during my senior year in the medical school at Johns Hopkins, when I was ill with typhoid. During those years he was in the middle period of his life, from the middle of his fifth to the middle of his sixth decade, a period regarding which Dr Osler, in his famous address, with facetious exaggeration, declared that a man's best work has then already been done, and that he is almost ready for euthanasia. In his own case, however, if old age was approaching, there was no sign of it. He had extraordinary energy, too much for the less vigorous assistants who followed him. He always arrived early and always promptly at the hospital and seemed not to walk, but to run, through the corridors. During the four hours or longer that he remained in the hospital, his mind as well as his body seemed always geared to high speed. What made the greatest impression on me was his perennial boyishness, combined with what seemed to me the learning and wisdom of a sage. He had an extraordinary power of attracting men to him, though exactly

why every one loved him so much is as difficult to say as why one does not love Dr Fell. One reason, undoubtedly, was that he had a great capacity for appreciating and loving his fellows. But he did not wear his heart on his sleeve, he was always kind, but never demonstrative. Moreover, if he did not approve of anyone, he practiced very strictly the virtue of taciturnity, so highly lauded by his hero, Sir Thomas Browne. He was never given to gossip. He could say

I am not one who much or oft delight
To season my fireside with personal talk

Paradoxically, he seemed to attract men by exhibiting a kind of reserve. He could, and frequently did, show flashes of the greatest familiarity, he could take the arm of the most exalted without arousing any resentment. But I never saw any one take his arm or slap him on the back. He was like a bird, mentally and physically—before one could catch him, he was up and away. He could convey more with a wave of his expressive hand than most men could with long disquisition. As he hurried through the private wards, women would be cheered for the day by a wave of his hand through the half-closed door. One day, seeing a box of candy at the bedside of a patient who he thought should not eat it, he picked up the box and, with a broad sweep, scattered the contents over the bed and about the room. The remarkable thing is that the patient did not resent it. She only laughed and thought it a great joke. But woe to an intern who would try to imitate such tricks! The patient would^b have driven him from the room.

The numerous portraits of Dr Osler reveal his striking appearance, and from the excellent biography by Cushing one may obtain a clear picture of his unusual personal qualities. No star of the stage, screen or television has more of that undefinable quality known as personality than had Dr Osler. But the effects of personality are exerted only on contemporaries. Like the art of the singer or other musician, or that of the actor, it cannot be perpetuated, and the memory of it soon grows dim. Even when combined with more substantial qualities, its effect is evanescent. If it were not for Boswell, Samuel Johnson, even with his striking personality, would now be a dim figure. To perpetuate the qualities of Johnson required the conjunction of two unusual personalities.

In the presence of exceptional and sacrificing devotion on the part of a husband or father, Dr Osler was wont to remind his students that there are more men saints than women saints. Some of his ardent admirers, on account of his love for his fellows, his sympathy for the sick and oppressed and his upright and virtuous life were almost ready to place Dr Osler himself in that category. But, good as he was, Dr Osler was hardly that saintly. In any case, few saints

are remembered very often or very long Even Saint Francis is usually recalled now, except by the very devout, only as a man who preached to the birds

Dr Osler had an excellent memory and had read widely, not only in medical writings, but in English literature of all kinds, including poetry, and much that he read he remembered His stock was not packed away on shelves, difficult to find, but much of it lay close to his hand, ready to be used at a moment's notice This permitted his writings and his conversation to be illuminated with apt phrases and witty and humorous quotations He had a fine taste and appreciation for the best in literature, and he had himself no small degree of literary skill This is well shown in his addresses and biographic sketches, which may be read over and over with never failing pleasure It is difficult to think of any other American, educator or physician, who could adorn an academic occasion so gracefully, with words not only so pleasant to hear but containing such sound and useful advice He had a skill for narrative and a sense of the dramatic When one reads his story of the martyrdom of Servetus, the horrible scene comes vividly before one, and one's heart is filled with pity and with deep admiration for such constancy If Osler had devoted himself to literary work, it is possible that he might have rivaled the contemporary physicians Oliver Wendell Holmes and Weir Mitchell It is questionable, however, whether he possessed as great originality and humor as Holmes, or as much imagination and poetic feeling as Mitchell But in any case, neither the volume of his literary work nor the merits of any particular examples of it are sufficient to give it a permanent place in general literature

He not only had a wide acquaintance with English literature, but he had read extensively in the work of the ancient writers How sound his classical learning was I am in no position to know or judge One doubts, however, whether it was of the same grade as that of his colleague at Johns Hopkins, who wrote

Asclepius was Apollo's chosen son,
But to that son he never lent his bow,
Nor did Hephaestus teach to forge his net,
Both secrets hath Imperial Osler won
His winged words straight to their quarry go
All hearts are holden by his meshes yet

One has a suspicion that it was Osler's winged words and the meshes in which he entangled the hearts of the members, as well as his scholarship, that caused the British Classical Association to make him president shortly before his death It was a great honor for a physician, especially for one born outside Great Britain, but was hardly sufficient to win him lasting fame

From his student days onward, Dr Osler was a student of the history of medicine, and he became an ardent collector of old medical books and of the literary productions of physicians of all ages. He infected others with his enthusiasm in that field, and he exerted a great influence in improving and enlarging medical libraries in this country and in promoting the cultural accomplishments of American physicians. So much has been written about him in this role, especially by those who were associated with him almost entirely in this connection, that one sometimes fears that in future years he may be remembered only as a bibliophile, and that people will forget that he was a physician.

He was, indeed, a very versatile man, and no doubt his versatility itself is an added reason for the perpetuation of his memory. On the other hand, he himself clearly recognized the dangers lurking in "the fatal fault of diffuseness, in which even genius is strangled," that fault from which he said his old teacher, Dr James Bovell, suffered "with a quadrilateral mind, which he kept spinning like a teetotum, one side was never kept uppermost for long at a time." It was probably due to the example of this man that although Dr Osler made frequent excursions into bypaths, none of them ever became the main highway, and he always returned to the road called medicine.

Although Dr Osler is now being remembered by his students, friends and associates for one or another, or for all, of the qualities mentioned, in my opinion he deserves and will have a permanent place in history for other reasons. It has been said that if Shakespeare had not been caught poaching he would have become a butcher or a wool merchant of Stratford. Likewise, it is not improbable that if Osler had not "got the sack," as he called it, at the age of 15, for a minor misdemeanor during his school days at Dundas, Ontario, he would have followed in his father's footsteps and have ended up as a clergyman. Because of the prank he was transferred to another school, where he came in contact with two men who were to influence his entire life. One of them was his teacher, Rev W A Johnson, and the other was the medical director of the school, Dr James Bovell. It happened that both were enthusiastic students of natural history, in an amateurish way. Johnson was the possessor of a microscope, and as often as possible the men made excursions into the woods, making collections of the lower forms of animal and plant life and bringing their spoils home to be examined under the microscope. Soon after his arrival at the school, the young Osler began joining them on their collecting expeditions and sharing in their studies. Soon he was as enthusiastic as they were, and he filled his notebooks with careful records of the observations he made, not only with his unaided eyes, but through the microscope. He also made thin sections of tissues

and examined them under the microscope. When he was 19 he began his "ink pot" career by publishing, in a popular nature study magazine, a description of the "living things" which he was able to identify in a bottle of water collected from a spring. Two years later he published a more finished article on Diatomaceae, giving the results of his own observations. At the same time he was busy collecting and describing animal parasites which he found in the intestines of animals. Thus, early in life, he formed the habit of observing carefully and describing clearly what he saw, and this became the dominant characteristic of his work in medicine during the remainder of his life. At that time the generalizations of Darwin were giving rise to much controversy, and most of the studies of nature were influenced by the speculations of Lyell and Huxley and Herbert Spencer. But Osler was apparently little influenced by all these theories, and he confined his attention to the description of what he actually saw. He had curiosity, which is the mainspring of all scientific work, but his curiosity about any subject was not sufficient to make him attempt to determine the meaning or significance of what he saw, or to enter into theoretic discussions.

As he continued in his medical studies, he transferred his interest from the description of the lower forms of animal life to a description of the changes which may be observed in the human body as a result of injuries of various sorts, that is the process known as disease. Most students of disease, from Galen onward, had not only made inaccurate and slipshod observations and equally faulty descriptions but, on the basis of them and of the even more incorrect observations and descriptions made by their predecessors, were forever constructing theories, erecting systems and devising therapeutic procedures. Even Thomas Sydenham, who for two hundred years was the ideal of English physicians, was never such an accurate and strictly objective observer as was Osler, although he made some clever, rough descriptions of the features of certain diseases. Most of Sydenham's descriptions were based on vague impressions and on the authority of others, and in all his writings there is rarely to be found any description of actual examples of the conditions which he described. A great advance was made in the description of the features of particular diseases when in the nineteenth century, Pierre Louis began to employ the so-called statistical method in the study of diseases. Osler owed much to Louis, but statistics are of value only in proportion to the accuracy of the observations on which the statistics are based, and that is particularly true when the number of examples is limited, as must, of necessity, usually be the case when diseases in man are under consideration. Dr. Osler was not the first to make painstaking observations and to keep accurate records, but before his time there had been few physicians,

if any, who had so systematically and extensively employed that method. He did not confine his observations to the changes occurring in the external appearance of the patient, and to the disturbances in function, as manifested by such alterations as those in the body temperature and the pulse and respiratory rates, but from the beginning of his studies of disease he observed and described the appearance of the internal organs post mortem. He also employed to the fullest possible extent the mechanical aids which had been developed during the nineteenth century. After he came to Baltimore, he organized clinical laboratories in which gross changes occurring in the urine and blood during the course of disease might be observed and studied. In all his methods, he was attempting to describe the superficial and external features of disease more accurately than had previously been done. The time was not ripe, and neither was he equipped by training, nor had he the facilities available to attempt to describe disease in terms of the fundamental underlying sciences, such as chemistry, physics and mathematics. In no place, except to a slight extent in certain German clinics, was such investigation being done at that time. Within the limitations imposed on him, Dr. Osler succeeded in adding materially to knowledge concerning many diseases, including typhoid, pneumonia, the cerebral palsies of children, certain forms of diseases of the heart, the group of diseases in which erythema and other changes in the skin are present, and a large number of other conditions, too numerous to mention. He made no single discoveries of very great significance, but in every field in which he worked he added to knowledge. Besides numerous articles in which he presented the results of his observations, he wrote a textbook, in which he gave in brief form not only the results of his own studies, but also the most important observations made by previous writers. In deciding what was worthy of inclusion he exhibited great and just discrimination. Accuracy and conciseness of description were combined with a graceful literary style quite unusual in a book of this kind. Its importance was at once recognized, and it soon became one of the medical best sellers of all time. The publication of the book had one result not expected by the author. With characteristic honesty, he had included only those measures of treatment that had been proved useful by long experience. That was the only criterion that could be used at that time, for without further knowledge concerning the fundamental nature of most diseases, no rational basis for any proposed method of treatment could be employed. Some years later the book fell into the hands of a layman who was shocked by the deficiencies, realizing that they could be remedied only by obtaining more knowledge, he was instrumental in founding an institute for medical research the first to be established in this country.

The great talents of Dr Osler were well exhibited in his work as a teacher. He extended his influence and made the employment of his methods more widespread by developing and training members of his staff. The value of the intern system had been well demonstrated elsewhere, but Dr Osler saw that the short period of one or, at the most, two years of service, in vogue elsewhere, was not sufficiently long in which to train men in scholarly and scientific habits. By retaining the most capable men under his tutelage for longer periods, the best of them for five or six years, or even longer, it was possible to develop a group of men thoroughly trained in the methods of exact observation, who would themselves extend the boundaries of knowledge.

His greatest originality as a teacher was shown in his work with students who for the first time were coming into contact with patients. He taught them by joining in the examination of patients chosen at random, whom neither he nor the students had ever seen before. With no other aids, teacher and students attempted to learn all they could by observation alone. They employed the method of Zadíg, that of making deductions or inferences from inconspicuous features. The sessions, as exciting as following the trail of a murderer, were thrilling experiences for the students. Much was learned about the patient and even about mankind as well as of the disease concerned—an example of serendipity. Having arrived at a tentative diagnosis, the students were told how to look up the literature dealing with the condition, and they subsequently brought the material—often the original description—to class. The students were thus introduced to the best in medical literature. Careful records were kept by the students, and, after a number of patients with the same condition had been examined, a tabulation of the results by the students gave a composite picture, which served as an introduction to the statistical method. The student thus received much more than a preliminary training in diagnosis. Dr Osler was never greatly interested in nosology, but he recognized that the clinician “cannot live, speak or act without the concept of morbid categories.” Dr Osler’s ready wit helped to make the sessions most interesting and amusing, as well as instructive. Of course, there was a kind of showmanship in all this, but it was a very different kind of showmanship from that which was traditional among professors of medicine who assumed attitudes of profound gravity and unlimited learning and, pompously and with oratoric embellishments, gave lectures consisting mainly of medical aphorisms based on opinion and authority. Dr Osler employed none of these tricks. He rarely lectured, when he did so, he was not at his best.

The more advanced students spent most of their time in the wards, and Osler’s teaching there was always of the same informal character,

with the patient before him. In one of his addresses, he said, "I desire no other epitaph than the statement that I taught medical students in the wards, as I regard this as by far the most useful and important work I have been called upon to do." Dr. Osler, however, did not introduce bedside teaching. Over two hundred years before, Franciscus Sylvius had taught students beside his twelve beds in the hospital at Leyden, and he and his successors made that university a mecca for medical students from all over Europe. But never before the time of Dr. Osler had the students become a part of the ward organization or taken so active a share in the study of disease. It may be suspected that all this praise is colored by the memories of an ardent and enthusiastic disciple, but even at that time I was not an entirely blind disciple, and my admiration was a little clouded by the realization that methods other than observation and enumeration might be required to bring insight into the real nature of the various diseases. No doubt I was influenced by others, for that point of view was very much discussed during Dr. Osler's last years in Baltimore. Although I never heard him speak of the matter, he was undoubtedly thinking about it, and I had the feeling that one important reason for his decision to give up his work in investigation and teaching—his removal practically amounted to that—was that he felt the time to be ripe for the introduction of new methods into the study of disease. He was no chemist or physicist or mathematician, he was not even familiar with the technics of bacteriology. Questions were constantly arising that could be answered only by more fundamental investigations than could be carried out at the bedside or in the primitive clinical laboratories. It is not enough to study phenomena as they occur in nature, nature must be put in chains, and the phenomena must be studied under controlled conditions. Many men realized that if medicine were to retain its place as a real university discipline it must become experimental, as other sciences had done.

A few years after Dr. Osler's departure the matter became acute, but, unfortunately, the discussion revolved about the question of whether or not a professor of medicine should devote his whole time to teaching and investigation and discontinue private practice entirely. This discussion took the matter outside the point really at issue. It is true that much time is required to carry on investigations of great complexity, for many men all the time available is not sufficient. However, it was thought that by making more time available for the professors, more of them would be likely to become real investigators, and therefore it was argued, full time employment should be compulsory. Dr. Osler opposed this as an unjust restriction of liberty, and he feared that "clinical and laboratory seclusion" would result in lowering the

effectiveness of the teaching of professors of medicine. It is not difficult to understand his point of view. Although his own situation was not involved, it would have been difficult for him to be so completely objective as to disregard entirely how the proposed change would have affected him if it had taken place during his earlier years. He was not fitted either by temperament or by training to spend a considerable part of his time in experimental studies. He could not view with equanimity any impediments to those contacts with men, patients and friends, in which he so greatly delighted. He was a humanist as well as a scientist. The terms are not mutually exclusive, though they are sometimes so regarded. One can be a disciple of Plato and at the same time of Aristotle, although Dr Osler once intimated that he preferred to be a follower of the former. His attitude toward science is shown by a statement in an address which he delivered soon after he went to Oxford. He said that the old universities had slept for years "after science had cried her message from the house tops—awake! awake! for the light has come!"

The experience of the past forty years, with the great increase in knowledge that has taken place and the improvement in teaching that has occurred, indicates that he was mistaken in his stand on the question of full time work, but that fact should not detract from the appreciation of what he accomplished with the older methods. Indeed, the change was made possible by his own work as an investigator and a teacher, and its consummation was greatly hastened by the improvements in the organization of the clinic which he introduced at Baltimore. That his opinion concerning this matter was later modified is shown by the fact that shortly before his death he addressed a letter to his alma mater in which he advised that "whole time (or if thought wise, largely so) heads of clinics should be appointed."

In most university departments of medicine, the study of disease has become much more intensive than it was fifty years ago. One may recall the famous answer of John Hunter to Jenner, "Why think? Why not try?" If Dr Osler had been asked the same question, he might have answered, "Why think? Why not look?" Today the ideal reply would be, "Why not think, look and try?" for without preliminary hypotheses experimentation is like shooting in the dark. Looking, during the course of an experiment, is also of the greatest importance. Neglect of this factor is one of the reasons that so much experimentation is futile. Experimentation is one way—probably the surest and quickest—of arriving at the truth, but it is not the only way. A great part of present knowledge was obtained by the methods employed by Dr Osler. Anatomy and pathologic anatomy were, until very recently, purely descriptive sciences. Even in Harvey's great demonstration, experimentation did not play the entire role.

Even before Dr Osler's death there had been a tendency to deny that he was a scientist at all, and to say that he was a clever diagnostician, an exploiter of the deductive method, an artist engaged in the practice of medicine. To claim that he was not a scientist is as absurd and misleading as to say that medicine is not a science. The methods that he employed are still of great importance in the study of disease, if they are neglected, medical progress will be delayed.

In my opinion, it is as a scientist who made important contributions to the science of medicine, and as a teacher of the subject, that Dr Osler deserves our highest appreciation, and it is for these reasons that he will forever remain an important figure in the history of medicine. It must be remembered that Posterity is an unpredictable jade, and that she often distributes her favors for qualities that are not the most deserving and, indeed, may refuse entirely to grant them, even for the most meritorious deeds, but I am convinced that his merits as a scientist and teacher were so outstanding that he will always be included among the Masters of Medicine.



A, Osler finishing his work" at the Philadelphia Hospital, 1889 B, Osler working on the first edition of his textbook at the Johns Hopkins, July 1891 C, Osler, his nephew W W Francis, Dr William S Thayer and Dr H A Lafleur in Lafleur's room at the Johns Hopkins, just before his return to Montreal in 1891 Dr Francis writes "Note the cat and the battered top hat on the table The cat was a dysenteric nuisance, but certified nonamebic O had decided that the hat was not respectable enough for Montreal so he and I had played football with it"



Second dinner of the Residents' Association, Johns Hopkins Hospital, 1892
 1, G H F Nuttall, bacteriology, 2, Simon Flexner, 3, William T Councilman, pathology, 4, A A Ghriskey, surgeon, 5, A C Abbott, bacteriology, 6, Hunter Robb, gynecology, 7, Sir William Osler, 8, Howard A Kelly, 9, Henry M Hurd, superintendent, 10, A L Stavelly, gynecology, 11, E M Parker, surgery (or pathology), 12, W H Baltzell, surgery, 13, John P Lotsy, plant pathology (working under Dr Welch), 14, William Wood Russell, gynecology, 15, John Hewetson, medicine, 16, Thomas S Cullen, gynecology, 17, August Hoch, psychiatry, 18, E McE Van Ness, histology, 19, John M T Finney, surgery, 20, William Sydney Thayer, 21, H Phippen, 22, John Goodrich Clark, gynecology, 23, Lewellys F Barker, medicine, 24, Frank R Smith, medicine



Osler, about 1900



Print of frontispiece from C N B Camac's "Counsels and Ideals from the Writings of Sir Wilham Osler" (ed 2, Boston, Houghton Mifflin Company, 1921)
Taken at Osler's desk at 1 West Franklin Street, his home in Baltimore



A, Dr George Dock, Mrs Osler and Dr Osler in the Netherlands in 1901
B, Osler on a porch at Murray Bay, Quebec, 1902



A, Osler in the Saturday clinic for third and fourth year students at Johns Hopkins, about 1902 B and C, at the bedside in Johns Hopkins, deliberating, and quizzing a student, about 1903



Osler looking savage at an artist's sitting (1905)



Sargent's painting of Osler, Welch, Kelly and Halsted Photograph lent by
Dr Wilburt C Davison

EXCERPTS FROM OSLER

A Mosaic of Bedside Aphorisms and Writings

WILLIAM BENNETT BEAN, M.D.

IOWA CITY

TO MANY who did not come under the direct influence of William Osler, his impact on physicians of his period has been something of a mystery. Those who knew him at first hand, and this included all who knew him even briefly, so warm was the glow of his presence, were a devoted, almost an apostolic band. If their zeal was at times overlavish, their motivation was honest. To the present generation of physicians, whose sharp focus on the mundane aspect of science has dulled the appetite for hero worship and who pay scant tribute to the great spirits of their own time, a pause to look backward may bring some insight into the personality of a noble physician, whose greatness lay in what he was rather than in what he did. How better than by his words can we know him?

A collection of bedside epigrams,¹ the "oslerisms" of many a student, came to me after my father's death. They had once been prepared for publication but were withdrawn after the publicity attending the misunderstanding of Osler's "Fixed Period" address. I have had the pleasant task, in ever diminishing spare moments, of seeing how many of these epigrams were used before or after that time in Osler's printed addresses, and the more difficult task of seeking certain original sources, for there are direct quotations or paraphrases from Burton, Browne, Fuller and other favorites. Indeed, Cushing attributed one of Thomas Browne's passages from the "Religio medici" to Osler.² But the time is now ripe for celebrating the centennial of Osler's birth, which justifies presenting this fragment as it is. The complete collection will be published at some future date.

THE UNDERGRADUATE STUDENT

The very first step towards success in any occupation is to become interested in it.³

1 Bean, R. B. Bedside Aphorisms of William Osler Collected as a Student, 1903-1905, to be published.

2 Cushing, H. Life of Sir William Osler, Oxford, Clarendon Press 1926.

3 Osler, W. The Master-Word in Medicine, Montreal M. J. 32 771, 1903.*

* Reprinted in Aequanimitas and Other Addresses, Oxford University Press, 1905.

In seeking absolute truth we aim at the unattainable, and must be content with finding broken portions ⁴

The value of experience is not in seeing much, but in seeing wisely ⁵

The good observer is not limited to the large hospital ⁶

Half of us are blind, few of us feel, and we are all deaf ¹

Don't touch the patient—state first what you see, cultivate your powers of observation ²

What can one hear with one's fingers? Vocal fremitus and a sharp second sound ¹

(Of a patient who said he had had jaundice at the age of 12) Infantile memories are fallacious ¹

Care more particularly for the individual patient than for the special features of the disease ²

As no two faces, so no two cases are alike in all respects, and unfortunately it is not only the disease itself which is so varied, but the subjects themselves have peculiarities which modify its action ⁷

There are no straight backs, no symmetrical faces, many wry noses, and no even legs We are a crooked and perverse generation ¹

We can only instil principles, put the student in the right path, give him methods, teach him how to study, and early to discern between essentials and non-essentials Perfect happiness for student and teacher will come with the abolition of examinations, which are stumbling-blocks and rocks of offense in the pathway of the true student ⁸

Education is a life-long process, in which the student can only make a beginning during his college course ⁸

Do not waste the hours of daylight in listening to that which you may read by night ⁶

Great minds are preeminently good or bad, and education makes them better or worse ¹

So long as we have human beings for house officers, ordinary mortals for medical students, and modified angels for nurses, we shall have typhoid contagion from one patient to another in the wards of our hospitals ¹

One can weigh the secretions in the balance and measure the work of the heart in foot-pounds ¹

The type of school I have always felt the Hospital should be a place of refuge for the sick poor of the city—a place where the best that is known is taught to a group of the best students—a place where new thought is materialized in research—a school where men are encouraged to base the art upon the science of medicine—a foundation to which teachers in every subject would come for inspiration—a place with a hearty welcome to every practitioner who seeks help—a consulting center for the whole country in cases of obscurity ²

4 Osler, W *Æquanimitas* Valedictory Remarks to the Graduates in Medicine of the University of Pennsylvania, May 1, 1889, Philadelphia, W F Fell & Co, 1889 *

5 Osler, W The Army Surgeon, *M News* **64** 318, 1894 *

6 Thayer, W S Osler, the Teacher, *Bull Johns Hopkins Hosp* **30** 198, 1919

7 Osler, W Teaching and Thinking The Two Functions of a Medical School, *Montreal M J* **23** 561, 1894-1895 *

8 Osler, W After Twenty-Five Years, *Montreal M J* **28** 823, 1899 *

THE STUDENT PRACTITIONER

Given the sacred hunger and proper preliminary training, the student-practitioner requires at least three things with which to stimulate and maintain his education, a note-book, a library, and a quinquennial brain-dusting⁹

But by the neglect of the study of the humanities, which has been far too general, the profession loses a very precious quality¹⁰

There are only two sorts of doctors those who practice with their brains, and those who practice with their tongues⁷

Common sense in matters medical is rare, and is usually in inverse ratio to the degree of education⁷

The incessant concentration of thought upon one subject, however interesting, tethers a man's mind in a narrow field¹¹

The physician without physiology and chemistry practices a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which⁷

A physician who treats himself has a fool for a patient¹

The ease with which our minds fall into the ruts of one or two experiences¹²

THE ART OF MEDICINE

Medicine is a science of uncertainty and an art of probability¹

Probability is the rule of life, especially under the skin Never make a positive diagnosis¹

Taking a lady's hand gives her confidence in her physician¹

The man who dissolves gallstones is half brother to the one who aborts typhoid fever or pneumonia¹

Patients should have rest, food, fresh air, and exercise—the quadrangle of health¹

Absolute diagnoses are unsafe, are made at the expense of the conscience¹

Look wise, say nothing, and grunt¹

Speech was given to conceal thought¹

Often this ignorance must be very tantalizing, but it is more wholesome than an assurance which rests on a thin veneer of knowledge¹³

Believe nothing that you see in the newspapers—they have done more to create dissatisfaction than all other agencies If you see anything in them that you know is true, begin to doubt it at once¹

Live a simple and temperate life, that you may give all your powers to your profession⁶

CLINICAL APHORISMS

To talk of diseases is sort of Arabian Nights' entertainment¹³

Things medical and gruesome have a singular attraction for many people¹³

The physiognomy of disease is learned slowly¹⁴

9 Osler, W The Student Life A Farewell Address to Canadian and American Medical Students, *M News* **87** 625, 1905

10 Osler, W British Medicine in Greater Britain, *Montreal M J* **26** 186, 1897 *

11 Osler, W Chauvinism in Medicine, *Montreal M J* **31** 684, 1902 *

12 Osler, W Teacher and Student, Baltimore, J Murphy & Co, 1892 *

13 Osler, W Nurse and Patient, Baltimore, J Murphy & Co, 1897 *

14 Osler, W On the Educational Value of the Medical Society, *Boston M & S J* **148** 275, 1903 *

Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you ¹⁵

Alcoholism or coma? Better admit a patient to the hospital dead drunk than turn him away, to be discharged from the jail dead sober a little later ¹

The normal man walks by faith, the tabetic by sight ¹

Temperature charts—typhoid fever has a "Pennsylvania Railway-like" directness, in distinction to the zigzag "Baltimore and Ohio" chart of aestivo-autumnal fever ¹

I do not know at what age one dare call a woman a spinster ¹³

There are incurable diseases in medicine, incorrigible vices in the ministry, insoluble cases in law (Thomas Browne) ¹⁶

Common-sense nerve fibers are seldom medullated before 40—they are never seen even with a microscope before 20 ¹

Anesthetics and antiseptics have manacled the demon pain, and the curse of travail has been lifted from the soul of women ¹

Excretion is difficult after 40, absorption before 20 ¹

Soap and water and common sense are the best disinfectants ¹

The pharynx is the garbage dump of the bronchial tubes and nasal passages. The street sweepers (ciliated epithelial cells) are constantly on duty and especially busy at night removing the debris from the air passages, to be carried away the next morning ¹

The physics of a man's circulation are the physics of the waterworks of the town in which he lives, but once out of gear, you cannot apply the same rules for the repair of the one as of the other ¹⁴

Huge blocks of coal that would grace the doorstep of any multimillionaire coal dealer as a sign are carried into the lungs from our coal-polluted air, and tubercle bacilli ride in on coal black chargers three abreast. Coal barges equal to those on the Susquehanna are constantly passing through unbroken mucosa and along lymph ducts to the bronchial lymph nodes ¹

Man should go out of this world as he came in—chiefly on milk ¹

Lavage is often as beneficial to the cerebral ventricles as to the abdominal ventricle ¹

The mental kidney, more often than the abdominal, is the one that floats ¹

Total abstinence varies in different communities. South of the Mason and Dixon line a mint julep, a toddy, or a cocktail before meals or between is total abstinence, and a profusion of eggnogs at Christmas a necessity ¹

More people are killed by overeating and drinking than by the sword ¹⁷

Bacchus hasn't a ghost of a chance against a good backing of Scotch Presbyterianism ¹

PHILOSOPHY

A rare and precious gift is the art of detachment ¹¹

A cheerful man at the breakfast table is a great annoyance to his grouchy neighbor ¹

¹⁵ Osler, W. Internal Medicine as a Vocation, *M. News* 71 660, 1897 *

¹⁶ Bean ¹ Cushing ²

¹⁷ Osler, W. The Past Century Its Progress in Great Subjects, Medicine, *The New York Sun*, Jan 27, 1901 *

Amid the racket and hurly-burly few of us have the chance to warm both hands at the fire of life ¹⁸

The blessed faculty of forgetting ⁸

He who follows another sees nothing, learns nothing, nay, seeks nothing ¹

The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow ¹¹

Advice is sought to confirm a position already taken ²

To know just what has to be done, then to do it, comprises the whole philosophy of practical life ¹⁰

In seeking absolute truth we aim at the unattainable, and must be content with broken portions ¹

The greater the ignorance the greater the dogmatism ¹¹

Happiness lies in the absorption in some vocation which satisfies the soul ¹⁹

Variability is the law of life ¹⁴

When schemes are laid in advance, it is surprising how often the circumstances fit in with them ¹⁵

Quite as much "grit" and a much harder climb are needed to reach distinction from the top as from the bottom of the social scale ²⁰

"THE GREAT REPUBLIC OF MEDICINE"

The great republic of medicine knows and has known no national boundaries ²¹

There is no more potent antidote to the corroding influence of mammon than the presence in the community of a body of men devoted to science ¹

Modern science has made to almost everyone of you the present of a few years ⁷

In science the credit goes to the man who convinces the world not to the man to whom the idea occurs first ²

It is strange how the memory of a man may float to posterity on what he would have himself regarded as the most trifling of his works ²

EPITAPH

I taught medical students in the wards ²²

University Hospitals

18 Osler, W Weir Mitchell Remarks on the Occasion of the presentation to the College of Physicians, Philadelphia, of the Portrait of Dr S Weir Mitchell, April 22, 1890, Johns Hopkins Hosp Bull **1** 64, 1889-1890

19 Osler, W Doctor and Nurse Remarks to the First Class of Graduates from the Training School for Nurses at the Johns Hopkins Hospital, Baltimore, J Murphy & Co, 1891

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OSLER RECOLLECTIONS OF AN UNDERGRADUATE MEDICAL STUDENT AT JOHNS HOPKINS

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IT IS PLEASANT as one grows old to turn the leaves of the book of personal memories and to relive the days of fifty years ago, even if some of the memory pictures of the past seem a bit hazy when one tries to conjure them back into reality. Memories of the past concern themselves with both personalities and events. For me personalities dominate memories of the past, and I can envision persons as they had a part in the activities of my bygone days better than I can envision events. Thus, with the eyes and ears of an undergraduate student of medicine at the Johns Hopkins in the late nineties, when I was a member of the fourth class to enter that institution, I can again see and hear Osler, with his dynamic, picturesque personality.

How did Osler teach medicine at that time to the beginner? What was the secret of his great influence on students? He gave no didactic lectures. He held no recitations. He assigned no routine of reading. His contacts with students were (a) in two weekly clinics, one for the third year and one for both the third and the fourth year class, (b) in three ward visits a week for two months in the fourth year for the quarter of the class serving as clinical clerks, and (c) at a weekly evening meeting at his home with the same students. In my time the groups contained ten or eleven students.

The teaching was described in the school catalogue:

Third Year General Symptomatology of Disease. At twelve o'clock on Tuesdays, Thursdays and Saturdays Dr. Osler meets the students in the class room adjoining the Dispensary. The students in rotation examine selected cases. The teaching consists in (a) thorough consideration of the clinical features of the case, (b) brief discussion of the symptoms, (c) reports by each student upon the cases which he examines and whose further progress he follows either by personal visits outside or, if the patient is admitted to the Hospital, by observation in the wards, (d) on the last day of each month a clinical "round-up," when the student, whose turn it happens to be, reports on the work of the month, (e) short papers on definite themes given to the students relating to subjects which come up in the course of the examination of patients. These "five minute" papers on various topics familiarize the student with the literature and very often prove most instructive to the class and indeed to the teachers.

The class is taken frequently to the autopsy room and points in medical anatomy are demonstrated, questions on this subject also being set throughout the session

Clinics On Wednesdays at 12 Dr Osler meets the third and fourth year students in the clinical amphitheatre of the Hospital. Chiefly acute diseases are shown and discussed. Week by week, throughout the session, the progress of the cases shown is reported, and in the more important affections, as typhoid fever and pneumonia, an attempt is made to present in orderly sequence the entire experience of the session. In this way each student during the third and fourth years gets a valuable body of clinical experience. The deaths of the week are discussed, the autopsy report read, and the specimens shown.

Fourth Year Ward Work Of the four groups into which the class is divided the members of each serve for two months as clinical clerks in the medical wards of the Hospital. A certain number of beds are assigned to each student. He takes the history of the new case, keeps the notes, and, under the guidance and direction of the house-physician, makes the necessary examinations. The clinical clerks have access to the wards from 8 a.m. to 6 p.m. They accompany Dr Osler in the ward visits, read the histories of the new cases, are questioned as to the results of their examinations, and receive special instruction. In this personal contact of student with patient clinical instruction finds its rational development.

Ward Classes At 9 a.m. the ward visit is made on Tuesdays, Thursdays and Saturdays by Dr Osler. The members of the class are taught in the methods of examination, the progress of the case is followed, and instruction is given in the methods of treatment.

Clinics At 12 o'clock on Wednesdays the fourth year students attend the general medical clinic in the amphitheatre.

Thus were described Dr Osler's methods of teaching medicine. He dominated the students' clinical instruction at the Johns Hopkins. This was a dominance of personality, for there seemed a complete lack of what might be called the machinery of pedagogics. Each student was free to attend or not to attend teaching exercises. There were a few recitations on assigned parts of the Osler textbook (exercises given by one of the assistants, Dr Thayer or Dr Jacobs, during the periods of assignment of students to the department of medicine), but they were not taken by student or instructor as other than a means to learn a bit more of medicine. Attendance records, marks, examinations, when they existed, were but trivia to the student. However, with this method, or lack of method, each student was acquiring a vivid knowledge of medicine and, most important, was learning how to study the subject in a way which was to make of him a student of medicine for life.

Dr Osler as he appeared to and influenced undergraduate medical students at Johns Hopkins a half-century ago can be pictured best by a description of him in each of these four student contacts.

The third year dispensary clinic lasted one hour. It was held weekly, in a small room to which a patient was brought. Dr Osler sat at a medium-sized table or, often, informally on the table swinging

his legs. The patient reclined on a willowwork couch with an elevated headrest, in front of the table. On each side and at the foot of the couch sat students. A student had acted as clinical clerk in the dispensary to the patient to be discussed and had taken the history, made the physical examination and studied the blood and urine. The student presented to Dr. Osler the data that he had obtained. Dr. Osler queried and often examined the patient, demonstrating and discussing his own observations, and the clerk and the other students were queried.

Dr. Osler built up a vivid epitome of the disease under discussion, with emphasis, as illustrative of the condition, on special points in the patient's history and examination. Dr. Osler showed keen interest in the medical problem of the patient under study and often greatly enriched and enlivened the discussion by citing examples and incidents from his own wide clinical experience, to illuminate further to the students the subject under discussion. Usually there was reference to the literature of the subject, or possibly the discussion of recent or classic examples of the disease, but more often a suggestion to the student to go to the library and read for himself, so as to bring to a subsequent exercise a résumé of the literature, accompanied by the important books. This was facilitated by the library's location, in the main building of the hospital and almost in the path of the students as daily they went to and from their work, and by the fact that the doors of the library were never closed, day or night.

At each exercise, reports on patients previously seen were asked for, since each student was expected to keep track of his patients in subsequent visits to the dispensary, to the ward, if the patient was admitted, or by visits to the patient's home, if the patient failed to keep dispensary appointments. The patient was made to feel that he was helping in the education of medical students and that the student was his doctor, more interested in his welfare than was any one else. Dr. Osler always created a friendly atmosphere, and patients were willing to answer his questions and to do whatever he asked of them. The student was seeing in Dr. Osler a demonstration of the best sort of patient-physician relationship and was gaining invaluable preparation for his own independent clinical work.

Two incidents in my own experience in the third year dispensary clinic were illustrative of Dr. Osler's method of teaching. To me had been assigned a dispensary patient, a pale young woman with a story of easy fatigue and slight dyspnea. Examination of her blood showed anemia, with hemoglobin disproportionately low. She had chlorosis, a disease still not infrequently seen at the Hopkins during my student days. Dr. Osler commented on the patient's typical history and appearance, queried me as to my knowledge of chlorosis and asked how I would treat the condition. "With Bland's pills daily in increasing number,"

I answered This promptly brought from Dr Osler the questions "What are Blaud's pills?" "Who was Blaud?" "When was iron first used in medicine?" I could give only very general and unsatisfactory answers, so Dr Osler said, "Christian, look the subjects up and report to us at a later meeting" Now I was involved in a library study, which eventually took me to Washington for a day in the Surgeon General's Library before I was ready to report Eventually my report was the basis of an article¹ published several years later in the *Medical Library and Historical Journal* That was the way Dr Osler had of introducing students to the use of the library and to contributing to medical literature It was my second stimulus in that direction, for in my first year Dr Mall had used my findings of an anomalous muscle in dissection to stimulate me to write a paper² which was published in the *Bulletin of the Johns Hopkins Hospital* before I had begun my clinical years in the medical school

At another of the dispensary clinics it fell to my lot to demonstrate the case of a young man who frequently had come to the dispensary, as well as been a patient several times in the hospital wards He was deeply jaundiced and had a large liver and many angiectases in his nose, which bled frequently and profusely His condition had been diagnosed as Hanot's cirrhosis His brother, a little older, had the same disease The patient had devised a very simple way to control his nose bleeds He took a thin rubber finger cot, put into its end a small cork, through which passed a small glass tube, and to the glass tube he had attached a bit of thin-walled rubber tubing He would insert the finger cot well into his bleeding nostril, expand it by blowing through the rubber tubing and clamp off the tubing between his teeth to keep the cot distended until its pressure stopped the nosebleed I had him demonstrate this to the section, while Dr Osler commented on how simple but ingenious methods might be useful to the physician and patient

Dr Osler had asked me to keep track of the patient, to report on his visits to the dispensary and to make follow-up visits at his home At a later clinic Dr Osler asked me how the patient was, and I replied, "I think he is about as usual I visited him about two weeks ago" With this, Dr Osler, to my embarrassment, dramatically brought forth a tray containing a large liver and other organs, saying, "Christian, he did not continue to do so well Dr MacCallum autopsied him this morning" That was the only liver showing Hanot's cirrhosis

1 Christian, H A A Sketch of the History of the Treatment of Chlorosis with Iron, *M Libr & Hist J* 1 176-180, 1903

2 Christian, H A Two Instances in Which the Musculus Sternalis Existed, One Associated with Other Anomalies, *Bull Johns Hopkins Hosp* 9 235-240, 1898

that I ever saw Obviously, it made a great impression on me, and for the subsequent fifty years I have diligently sought for another patient with similar cirrhosis of the liver, so far with no success

The weekly clinic in the amphitheater was attended by both students and graduate physicians In the front row, in a semicircle at floor level, sat the fourth year students then serving as clinical clerks in the medical wards Dr Osler sat at a table at one side, usually the audience's left On the blackboard there were always two tabulations, one of all patients with typhoid in the wards since the opening of the school year and the other, similar, of patients with pneumonia, with the important data on each patient Dr Osler always opened the clinic by having a student point to and comment on any addition of the week to the tabulations, and Dr Osler then had something to add, thus keeping continuously before the students facts about the two medical diseases, namely, typhoid and lobar pneumonia, which besides syphilis, he then regarded as of greatest importance to physicians

The presentation finished, a patient was wheeled in, his history and the report of his physical examination were given by the clinical clerk, and Dr Osler himself demonstrated and commented on the patient's condition, talked with him, usually giving him encouragement in terse, simple, easily remembered words, and then queried the clinical clerk in charge of the patient, as well as other clerks in that front semicircle One patient or several might be shown Finally Dr Osler talked, usually with the important bibliography on his table, and brought home to the audience, students and physicians, the salient features of the disease that had been illustrated That was Dr Osler at his best, and the students carried away a knowledge of the essential facts of the disease practically always with several epigrams which long would linger in his mind against the background of a visually remembered patient Dr Osler's charm, erudition, clinical wisdom and rapport with patients were such as to make of these clinics memorable examples of teaching

Ward rounds with Dr Osler were held three days a week, beginning at about 9 o'clock Dr Osler rarely missed being present to conduct them He would enter a ward trailed by his assistants, the resident physician, assistant residents, medical interns, clinical clerks from the fourth year class (the section of one fourth of the class assigned to medicine for two months) and usually visiting physicians He would go to a patient's bed, stand (or sometimes sit in a chair) near the head of the bed at the patient's right side, give him a cheery greeting and, if he were a new patient, ask for his history, which then would be given by the student clinical clerk After it had been commented on, possibly critized and often added to and illuminated by Dr Osler with accompanying pertinent remarks the report of the physical exami-

nation was called for from the clinical clerk. Often he was asked to demonstrate the features of the physical examination. Usually Dr Osler made some examination himself and demonstrated and discussed salient features, all the time mingling his discussion with remarks and explanations to the patient, so that he would not be mystified or frightened. Various members of the resident staff would be asked for reports of special examinations and for descriptions of changes and developments in the patient, witnessed in the ward by them. If others of the visiting staff had seen the patient, they were asked for comments and opinions. A visitor, often some prominent out-of-town physician, might be asked to comment or to give his opinion.

If the patient had been seen by Dr Osler on a previous ward visit, developments since then were reported by the clinical clerk, inquired about and commented on, possibly new features in the case would be demonstrated by the clinical clerk or by Dr Osler. Often patients whose cases had previously been discussed were passed over quickly, but Dr Osler never failed to give some bright, cheering words to the patient.

Ward visits were an unusual combination of informality and dignity. Students and patients quickly were put at ease by Dr Osler. The discussions seemed very informal, possibly a bit haphazard, yet a surprisingly complete description of the patient and his disease was left with the students. The combination of informality and dignity in the ward visits probably mirrored the similar combination which was so evident in Dr Osler's own personality. In his frock coat and with his scrupulously neat appearance, he was typically the consulting physician, honored and esteemed by all who came in contact with him, but there was no austerity in this. His twinkling eye, his quick steps, his frequent quips, his friendliness of manner, his habit of putting a hand on the shoulder of assistants, students and friends as he walked and talked, all brought into his clinics and ward visits a delightful tone of friendly informality. His criticisms of students and their work were incisive and unforgettable, but never harsh or unkindly, they inspired respect and affection, never fear.

The fourth of Dr Osler's contacts with Johns Hopkins undergraduate medical students was in his home, at 1 West Franklin Street, where the section of the class serving as clinical clerks went on Friday evenings at about 8:30 to sit around his dining table, with Dr Osler at the head. Interesting developments in the wards were talked about, recent papers were reviewed, books, old and new, were brought from his library shelves, medical history was discussed. Beer, crackers and cheese were at hand. All was informal. Nothing had been especially prepared by the clerks in anticipation, for none knew in advance what Dr Osler would bring up for discussion. In no sense was this evening a quiz to the students, all of whom felt free to answer and to report. It was

for them a delightful social contact with a great man in the charming, informal setting of his home, where he was host to a small group of young men who were skilfully being guided into a useful knowledge of medicine and of the paths to follow in future years toward true scholarship in that subject. Those evenings at 1 West Franklin Street, particularly, laid in the student's minds foundations of an interest in medical history. So skilfully did Dr. Osler weave into his discussions the importance of medical history, and so entertaining and interesting did he make it, that many of the students continued an active interest in the subject through life, and numerous of them made notable contributions to it.

Was Dr. Osler's way of teaching medicine a planned method, or was it merely a natural outgrowth of the Baltimore environment of those days of fifty years ago and of his own way of learning medicine? As I look backward, the latter seems to me to be the proper explanation. Others in this number of the *ARCHIVES* have described Dr. Osler's methods of instruction at Montreal and Philadelphia and have let us see, through comparison, how he changed his teaching after going to Baltimore. There had been a ten year interval between the opening of the Johns Hopkins Hospital and the opening of the Johns Hopkins Medical School, during which time Dr. Osler had done no undergraduate medical teaching. At the time in Baltimore that I have described, the medical school was only three and four years old, the classes were small, the students all were college trained, with special attention to the biologic, chemical and physical sciences, and with a reading knowledge of French and German, new methods of instruction were under trial in all departments of the medical school, the professors were relatively young men, the spirit of investigation was in the air. Could there have been a better background against which to try out ways of teaching? The environment and Dr. Osler's own training must have been important factors in his selection of methods of teaching medicine. His own personality, his extensive clinical experience, his writing of the textbook, "*The Principles and Practice of Medicine*"³ in his early days as physician in chief to the Johns Hopkins Hospital, and his scholarship and erudition seem to have been ideally suited to his way of teaching, which in final analysis was a natural, unstudied leadership of students, an unconscious giving of himself to them, combined with their unconscious recognition that in him they had a leader worthy to follow.

20 Chapel Street

3 Osler, W. *The Principles and Practice of Medicine*, New York: D. Appleton & Co., 1892.

MY FIRST MEDICAL CLINIC WITH DR OSLER

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TRADITION at the Johns Hopkins medical school was that Dr Osler's weekly medical clinic was to be attended by the house staff, by senior and junior students, and by other students only when space in back was available. The first row, consisting of chairs in front of the regular benches, was occupied by the interns, residents and visiting physicians. The other seats in front were reserved for the fourth year students, and the members of the third year class followed. They usually filled the amphitheater.

Toward the end of my second year in medical school, I left the hospital library one day, hoping to find room to attend Dr Osler's clinic. In walking down the corridor toward the amphitheater, with a notebook in hand, I went slowly, to reach the amphitheater after the others were seated. This being my first clinic, I was conscious that I must not violate any tradition. While sauntering along, I heard many voices and footsteps. I recognized the voice of Dr Osler, moved to the outer side of the corridor and slowed my pace a little. Just before I got to the entrance of the amphitheater, some one came up and ran his arm through mine and asked where I was going. I looked up, and, behold, there was Dr Osler! I told him I had started toward the pathologic laboratory, and he said, "Why go there? I thought you might be coming to my clinic." I said, "Dr Osler, I'm not yet a third year medical student." "All the better. Come along with me." I looked around, and with Dr Osler there were Drs Thomas McCrae, Rufus Cole and Campbell Howard, together with a few other physicians and the usual quota of interns. I told him I thought I had better go along, but he said no, that I should come in to the clinic and see what it was about. I went along with him, arm in arm, into the amphitheater, and he pointed to a chair in front, for me. There was not much I could say or much I could do, but I have never been so embarrassed in my life. I was not sure what the third and fourth year students would think. I was not particularly concerned about the second year students, but I shall never forget how I felt, walking in with Dr Osler and sitting down in the front row chair, with a notebook in my hand.

Dr Osler proceeded with his clinic. The patient happened to be a man who had fluid in the right side of the chest. Dr Osler discussed tuberculosis, demonstrating to me, seemingly, since I was so

conscious of being there that I thought he was looking at me all the time, and I was afraid that he might ask me some question. He demonstrated all the physical signs of fluid in the chest, and then he gave a talk on tuberculosis and tuberculous pleurisy, with effusion. I shall never forget that clinic.

After it was over, I attempted to get out as rapidly as possible, but Dr. Osler came over and told me he was glad that he had run into me, and he invited me to his clinics again. Curiously enough, there was no comment by any one about my presence at the clinic. I seemed to be the only one who had suffered. After that I did not hesitate to go to the clinics, but I always sat up on top, in the back rows. I came away impressed by the greatness of Dr. Osler, his sincerity, his simplicity, his love for mankind and his desire to be of help to others.

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AEQUANIMITAS

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IF SIR WILLIAM OSLER were to have summed up the philosophy of his life in a single word, it might well have been *aequanimitas*. It was the title he gave to his valedictory address at the University of Pennsylvania, and to his first book of essays¹. He practiced what he preached. Few men have acquired this quality of mind and soul in higher measure. It enabled him "to rise superior to the trials of life" and to meet little annoyances, as well as real sorrow, with serenity of mind. In the address, he impressed on his listeners the importance of cultivating the virtue of imperturbability, which he defined as "coolness and presence of mind under all circumstances." This quality, he pointed out, also enables its possessor to keep "his medullary centres under the highest control," so that his face will not lose its expression of serenity when annoying situations suddenly arise. "Don't feel the pinpricks!" and "Learn to consume your own smoke!" were maxims which he followed and which were expressive of the equanimity he had acquired.

An example of this quality of mind was his reaction to the incident of the chloroform. This was occasioned by his address, "The Fixed Period,"² delivered a few months before he left Baltimore for Oxford, in which he had stated two convictions. The first was that "the effective, moving, vitalizing work of the world is done between the ages of twenty-five and forty," and the second, that all teachers should retire at 60. He mentioned that Anthony Trollope, in one of his novels, urged the retiring of college professors at the age of 60, "for a year of contemplation before a peaceful departure by chloroform." Dr. Osler added that he had become a little dubious about advocating this practice, as his own time was getting so short (he was approaching his fifty-sixth birthday). He was cruelly mistreated by the press for making this allusion to chloroform. From one end of the country to the other, the newspapers spread the word that a Johns Hopkins professor advised death by chloroform at the age of 60. He was denounced, not only in the press, but also from the pulpit. The verb "to oslerize" was coined,

1 Osler, W. *Aequanimitas, with Other Addresses* ed. 3, Philadelphia, The Blakiston Company, 1932.

2 In Osler¹

meaning to chloroform the aging. For the first time in his eminent career, his name became widely known in lay circles, and then only in this connection. The following year he wrote, in the preface of the second edition of "Aequanimitas"¹ "To one who had all his life been devoted to old men, it was not a little distressing to be placarded in a world-wide way as their sworn enemy." At the time, however, he outwardly maintained his usual serenity. During the first week after the false statement had been given out by the reporters, I received a note from him, in which he wrote "I hope you are hurrying, as the years are flying and you will soon be forty." A few days later, I was visiting in his home and learned that even Mrs. Osler and his secretary did not know how he was taking the uproar of which he was the innocent cause, as he made no comment about it. The mail contained scores of denunciatory letters, but they were not shown to him. The only allusion to the incident he made to me was when he said, "The way of a joker is hard. I deserve to have been caught years ago."

While he was spending a few days in Boston, on one of his trips to this country, there was to be held some sort of open house at one of the hospitals, with demonstrations by members of the staff throughout the forenoon. I knew that the younger men would be eager to see and hear Dr. Osler, whose textbook was their medical bible. I asked Dr. Osler if he would be willing to speak at this informal gathering, and he readily accepted. I at once called the assistant superintendent, who expressed pleasure that Dr. Osler was willing to attend and take part in the exercises, but that afternoon the chairman of the program telephoned me to say that the program was prepared and that he was unwilling to ask any one to step aside and give his place to Dr. Osler. He reminded me that I was not on the committee and left me to get out of an awkward situation in the best way I could. I was unwilling to state the naked truth to Dr. Osler, so I talked with the acting dean of the medical school, Dr. Cannon, and suggested that Dr. Osler be invited to address the assembled students of the third year class at the close of the last afternoon lecture, to which he readily agreed. I then sought out Dr. Osler and told him that I had found that I could get a larger audience in the afternoon at the school, which was the truth, and asked if he would be willing to talk to the students. I watched his face anxiously as I put this question to him. His expression retained its usual serenity as he replied that it would suit him just as well. He made no questioning comment. That afternoon I took him to the school on a streetcar. The hour was rather late, I think it was 5 o'clock. He spoke for only ten or fifteen minutes. Dr. Reginald Fitz, president of the class, recalls that it was "a memorable occasion." Dr. Osler then had the tiresome trip by streetcar and train to Canton, Mass., where he was staying with his

mother-in-law How few men would have had sufficient equanimity to disregard this pinprick and to accept the substitute plan I suggested!

Later (in 1910), an incident occurred to which Cushing refers in his "Life of Sir William Osler,"³ as does Fitz in his delightful account of the ward rounds Osler made one morning at the Massachusetts General Hospital.⁴ After the visit and a luncheon in the South Station, Dr Osler boarded his train as soon as it was made up. While seated in the car with him for the fifteen or twenty minutes before the train started, I asked him if he knew that an article by him had recently been published in the *Woman's Home Companion*. He expressed surprise. I had recognized the article as the transcript of a lecture delivered a few years before in Dublin, Ireland, and published with other articles in a book entitled "Ireland's Crusade Against Tuberculosis," which had been issued by a women's organization under the leadership of Lady Aberdeen, the wife of the Lord-Lieutenant of Ireland. The article had not been copyrighted and was sold to the editor of the magazine, doubtless for a goodly sum, by a man who represented himself as Osler's literary agent. Dr Osler seemed interested, but not disturbed, although he had every right to be. "That explains," he said, "the letter I had from Bok, which I never answered." Edward Bok, the editor of the *Ladies' Home Journal*, had offered Osler \$1,000 for three articles on the health of the American woman. He said that he had thought of accepting the offer, as he saw nothing wrong in it, and added, "I could have used the money." However, because he thought that in England it might be looked on as below the dignity of a Regius professor to write for a popular magazine, he had decided to decline the invitation. In the letter that had puzzled him, Bok had stated that although Osler had scruples about writing for the *Ladies' Home Journal*, it was evident he had none when asked to make a contribution to another magazine.

He apparently was not disturbed by the loss of the money, by Bok's letter or by the thought of any unfavorable criticism which the article might arouse in England. As Cushing had never heard the story until I told it to him, it is evident that here again Osler consumed his own smoke.

In the index to Cushing's "Life of Sir William Osler" are thirty-six references under the heading, "practical jokes, pranks, &c." As Cushing says, his pranks, "an expression of his lively sense of fun, were what served to make him such a good companion." Egerton Yorrick Davis, like Sir James Barrie's M'Connachie, was the unruly

³ Cushing, H. Life of Sir William Osler, Oxford, The Clarendon Press, 1926.

⁴ Fitz, R. A Visit with Osler, New England J Med **234** 617, 1946.

half of his creator. In a note appended to a collection of documents relating to Davis in the Osler Library in Montreal, Osler stated that he had "often used his name when I did not wish to be known." I was present on one such occasion when Dr. Osler's fanciful double appeared. One evening in the spring of 1905, Dr. James G. Mumford, surgeon and well known medical historian, and I were standing with Dr. Osler on the platform of the Back Bay station, waiting for the Federal Express which was to take Osler to Baltimore, when a man approached our group and said, "Isn't this Dr. Osler?" "I am Dr. Davis," said Dr. Osler, "and these are my friends, Dr. Bigelow and Dr. Ware." He had bestowed on us the names of two of Boston's medical worthies of a century ago. The man looked puzzled but walked away without another word. We made no comment, and Dr. Osler offered no explanation.

This mischievous half of the great physician often got the upper hand and, although it furnished much entertainment to his friends, sometimes got him into trouble. "One of my favorite poets," Prof. B. L. Gildersleeve wrote, "commends turning the fair side outward—but in Osler's case it is hard to say which is the fairer, the jest or earnest." Dr. W. T. Councilman recalled in later years a favorite game which Osler had played at the dinner table of the Johns Hopkins Hospital in the early days, when both were in residence there. It was "to relate the impossible and to lead up to this so skilfully that the line between fact and fiction was obscured. It was very well for us who knew the game, but occasionally it would be played when the serious visitor was present and he often carried away with him striking information of new facts in medical science." Once I was present at a luncheon at the University Club in New York, which Dr. Osler gave during a meeting of the American Association of Pathologists and Bacteriologists. The other guests were Dr. Councilman, Dr. J. G. Adams, of McGill University, and Dr. William MacCallum, of Johns Hopkins. It was MacCallum who started Dr. Osler off by asking "the name of this delicious fish we are eating." "It is scrod," said Dr. Osler. "Scrod!" said Dr. MacCallum, "I never heard of it." "You know what a capon is, scrod is codfish that has received the same treatment. The production of scrod has become a thriving industry along the New England coast, as Councilman knows." Dr. Osler then went on to describe in detail how "the cod come up inlets from the sea in great numbers in the spring and are diverted into narrow, shallow troughs, from which they are removed by the nimble hands of trained workers, who quickly and skilfully castrate them. They are then placed in large vats or artificial pools of salt water. There, after a month or so, their flesh acquires a new and

improved flavor They are then shipped to market" MacCallum showed by his expression that he was deeply interested and thanked Dr Osler for giving him this information "It is most remarkable," he said, "and all new to me" None of the others made any comment, so MacCallum had no reason to doubt that this was a real addition to his store of knowledge

Later, while we were still at the table, Dr Osler gave a vivid description of a remarkable raid, made by Indians from Canada on a small Connecticut village in early Colonial days I thought it was a historical account until he mentioned the name of Elder Dempster as one of the victims, I then recalled that Elder Dempster was the name of a line of steamers that sailed between Montreal and Liverpool, but, as Dr Councilman remarked, it was difficult to tell where fact, if any, ended and fiction began

Osler often made a joking reply to a question when for any reason, he did not wish to give a serious answer In Vienna, during the meeting there of the German Congress of Internal Medicine in the spring of 1908, we attended a cabaret performance as guests of the Vienna Medical Society One of the features was a tableau of a Japanese garden, with beautiful young girls grouped around a fountain Possibly as a substitute for clothes, a diaphanous curtain was placed at the front of the stage Dr Osler sat at some distance from me When I caught his eye, he lifted his program in front of his face for a moment The next day a young American physician, evidently expecting a serious answer, asked Dr Osler at luncheon what he thought of the Japanese tableau given the previous evening Dr Osler said, "It was artistic, but Pratt, here, has been complaining that the powder was too thick on the ladies"

It was characteristic of Osler to omit the stereotyped greeting when he met a friend, even if he had not seen him for a long time Dr Reginald Fitz mentions this in his account of Osler's visit to the Massachusetts General Hospital³ I was making rounds with Fitz and two other interns when Osler, unexpected and unannounced, entered the ward, walking directly to the bed where we were examining a patient He had arrived from England a few days earlier, after a year's absence from this country "Instead of observing the amenities by commenting on the weather or the state of our health," says Fitz, "he immediately became part of us by asking, 'What have you here?'" Osler at once assumed charge of the visit, much to our delight, and gave a regular ward clinic, as had been his custom in Baltimore

Years before, in 1904, when Osler had visited the same hospital, I conducted him from the entrance to the Treadwell Library to meet the elder Dr Fitz We entered the library through a short corridor, on the wall of which, surrounded by the coats of visiting physicians,

was an oil painting of Louis, the great French teacher and inspirer of American students. Osler paused to examine the portrait. Then, as he entered the library, his first words were "Fitz, don't you realize that Louis is the patron saint of this hospital? His portrait should hang in the most prominent place you can find."

When I called on Osler at his home at 1 West Franklin Street, Baltimore, one day early in January 1905, he himself came to the door. I recall the words of his salutation because they were so unusual. "I have actual proof," he said, "that even a gynecologist may have moments of godliness. Come and see what [Dr. Howard A.] Kelly gave me Christmas!" He then led me into the front room on the left of the entrance, where, in a prominent place, were displayed the five volumes of the Aldine edition of Galen's works, printed in 1525. They are now one of the treasures of the Osler Library in Montreal and are described in "*Bibliotheca Osleriana*"⁵ on page 34.

Another example of his equanimity occurred on an occasion that would have been emotionally disturbing to most men. Cushing states:

On Sunday the 15th [of May 1905] Osler wrote his last notes from the corner of Franklin Street, and with a small handbag he left on the following morning for the meeting in Washington, leaving the bustle of packing-cases behind him, and escaping the sly remark that "Willie's motto may well be *aequanimitas* because he always flees when things like this are going on." He was not seen again by his family till they met for dinner three days later in New York.

By chance I was in his house that Sunday, copying some of his notes for an article I was preparing for his system of medicine.⁶ Late in the afternoon, when Mrs. Osler and he were to have tea, they asked me to join them. It was served in the breakfast room at the rear of the house, as the other rooms were filled with packing boxes. Tea that last day in his old home might well have been a somber occasion, but he was as gay as usual. "Almost never," as Cushing says, "did Osler betray his deeper feelings by any show of sentiment." I remember some of the conversation as though it were yesterday. Osler made some jocose remark about having reached the presenile age and remarked that, in consequence, his arteries were hardening. "But, Dr. Osler," I said, "you taught us that everything depends on the quality of the arterial rubber we inherit, and as your mother is living and well at 98, your arteries must be of the finest quality." "She didn't pour hot and rebellious liquors into her blood when she was young!" Dr. Osler replied. "Neither did you!" said Mrs. Osler, with

5 Osler, W. *Bibliotheca Osleriana. A Catalogue of Books Illustrating the History of Medicine and Science*, Oxford, Clarendon Press, 1929.

6 Osler, W., and McCrae, T. *Modern Medicine, Its Theory and Practice*, Philadelphia, Lea Brothers & Co., 1907.

a note of irritation in her voice. She evidently did not want me to think that I was listening to a confession of early dissipation. "Tut, tut, woman, what do you know about what I did in my youth?" he said, pointing a finger at his wife. "I know," I said, "because you would not have advised total abstinence to your students, as you did in the first valedictory address you gave in Montreal, if you drank yourself." "You are right," he admitted. "I never took any alcoholic drink until I went to Europe."

He lived up to his personal ideals as few men have done. At the great subscription dinner held at the old Waldorf-Astoria Hotel, shortly before his departure for Europe, his parting words dealt with his three ideals, the last of which was "to cultivate such a measure of equanimity as would enable me to bear success with humility, the affection of my friends without pride, and to be ready when the day of sorrow and grief came to meet it with the courage befitting a man."

30 Bennet Street (11)

RANDOM RECOLLECTIONS OF WILLIAM OSLER

1899-1918

WARFIELD T LONGCOPE, M D

Emeritus Professor of Medicine, Johns Hopkins University

LEE, MASS

OSLER gave his students at the Johns Hopkins such wise advice as "Don't trust your memory Make notes Write down your observations This is very important in cases of pericarditis Percuss carefully the limits of dulness, measure them Fluid may accumulate rapidly in the pericardial sac If you make measurements you can compare them every day, and then you will know whether the fluid is increasing or decreasing" The secret of teaching, he insisted, was repetition He used the method in the dispensary, in the wards and in his clinic, with such good effect that his admonitions and aphorisms, as well as his point of view and his attitude toward the study of disease, were indelibly impressed on the minds of his devoted pupils In consequence, perhaps, the daily routine of work in the medical clinic remains only as a blurred background, against which a few vivid pictures stand out, like photographic snapshots, in bold relief

A fact which now astonishes me is that no recollection remains of my first meeting with Osler On the other hand, it is possible, after almost fifty years, accurately to recall isolated glimpses of this fascinating figure, while single incidents remain impressed on my memory Even to this day I can see him, in top hat and gray morning coat, with a cane hanging on his arm, striding swiftly down the interminable hospital corridor with a swinging gait Invariably he would catch up with an assistant or student, take him by the arm and hurry him along at an unaccustomed pace toward the wards or the dispensary

At the informal clinic for the third year students, held in the dispensary, he often sat on the edge of a stout golden oak table, sometimes hanging one leg over the side From this slight elevation, he looked down on the patient, who lay on a wicker couch, with the back of his head toward Dr Osler Thus the patient heard what Dr Osler had to say but could not watch the changes of expression on his face We students sat in chairs with arm rests in a semicircle about the couch The arrangement must have been purposeful, for we could

watch the patient and see Dr Osler, who conveyed much information in the expression of his face and the movement of his hands, while himself hidden from the patient

A student took part in the examination of each patient and the discussion of the case Dr Osler frequently requested the student to consult books or articles on some detail pertinent to the disease under consideration, and to present his report at a subsequent meeting On one occasion, a member of the class was asked to examine a patient with situs transversus By a lucky guess, or through unexpected acumen, he arrived at the correct diagnosis and at a later session, much to the surprise of the Chief, quoted from "*Le médecin malgré lui*," in which Moliere makes an amusing reference to this unusual state of affairs ¹

Sganarelle, the pseudodoctor, examines Lucinde, the daughter of Geronte, and gives the following explanation of the illness

"Sganarelle Now, these vapeurs of which I have been speaking to you, in passing from the left side where the liver is, to the right side where the heart is, it happens that the lungs, which we call in latin "armyan," communicating with the brain, which we call in Greek "nasmus," by means of the concave vein, which we call in Hebrew, "cubile" meets on its way the said vapeurs, which fill the ventricles of the omoplate

"Geronte No reasoning could be better, I think, there is only one thing which struck me as not quite clear, it is the places you give to the liver and the heart It seems to me that you place them differently from what they really are, that the heart is on the left side and the liver on the right side

"Sganarelle Yes it was so formerly, but we have altered all that, and we now practice medicine in quite a new way

"Geronte I did not know that, and I beg you will excuse my ignorance

"Sganarelle There is no harm done, it cannot be expected that you should be as clever as we are"

This absurd conversation is derived from Moliere's familiarity with a case that was famous at the time the play was written A notorious criminal was executed The body was "dissected," and, to the amazement of the operators, a complete transposition of the viscera was discovered

On another day, a student who was keeping track of an elderly man with aortic insufficiency and angina pectoris, who had been shown at a previous clinic, stated that he had seen the patient at his home and had advised him to take hot baths With a quizzical expression and in a lugubrious voice, Dr Osler said, "Is there any danger, Mr —, in ordering hot baths for patients with aortic insufficiency and angina pectoris?" At that, the horrified student, fearing the worst,

1 Moliere (Poquelin, J B) The Dramatic Works of Moliere, translated into English prose with short introductions and explanatory notes by Charles Heron Wall, London, George Bell & Sons, 1901, vol 2, p 224

left the clinic in haste and dashed to the house of his patient, only to find the old man sitting on his doorstep, smoking a forbidden pipe. Of one young man, who was shown at a dispensary clinic on account of repeated attacks of appendicitis which had prevented him from working, Osler said, "This is an instance in which the tail wags the dog."

On ward rounds, Osler would often stand at the head of a patient's bed, gracefully using his beautifully shaped, small, brown hands, with their tapering fingers, to accentuate what he had to say. He was fond of enumerating, as first, second and third in order of probability, the situations in which such and such a condition might occur, frequently the last possibility was totally unexpected and entirely irrelevant. In examining a patient, he would sit at the side of the bed, watching the motions of the chest or abdomen and looking for moving shadows in different lights, to which procedure he attached great importance. He told the story of the nurse who, having detected the pulsations of an aneurysm in the chest wall of a patient, changed the position of the patient so that the light brought out the shadow of the localized impulse, which thus became readily visible to the astounded physician. Much time was also devoted to the palpation of the chest and abdomen. Osler was likely to use both hands and to point out the advantages of doing so.

While walking down the long wards, he sometimes stopped to grasp the toes of a patient. As he did so, he would remark that Oppolzer was in the habit of surprising his students by making the diagnosis of aortic insufficiency after feeling the toes of a patient from the foot of the bed. This impressed on us the importance of the "water-hammer pulse" as a sign of aortic insufficiency. To Vulcan and Venus he ascribed this malady, as well as aneurysm, which in those days was frequent in the wards of the Johns Hopkins Hospital.

The regular Saturday morning clinics were held at noon in the old amphitheater. The students sat on rising tiers of wooden benches. On the wall opposite the seats there were sliding blackboards. Several of these were reserved for recording data, throughout the year, concerning the course of at least two diseases as they affected the patients admitted to the wards. Every case of typhoid fever and every case of lobar pneumonia was tabulated in this manner. The students who were responsible for collecting and recording this information were thus able to follow the course of two important infections as they were observed during the entire time that the patients remained in the hospital. Dr. Osler laid much stress on the advantage of using graphic methods for presenting clinical observations and frequently referred in his clinics to these charts on the blackboards.

There was great excitement one day when Osler performed an autopsy. The case was one in which he had made the diagnosis of bilateral congenital cystic kidney. At that time the condition was rarely recognized during life, and on this account Dr Osler had asked Dr William H. Welch, as a great favor, to allow him to conduct the postmortem examination. The tiers of seats overlooking the autopsy table were crowded with members of the staff and with students, for the occasion was unique. Dr Osler, protected by a large apron, rolled up his sleeves and went about the job in a professional manner. The climax came when he removed from the abdomen two huge kidneys, filled with cysts.

Much of the instruction was carried on in an informal manner, the students always participated in one way or another. Perhaps the most intimate of the exercises were the weekly evening meetings in Osler's house at 1 West Franklin Street. In addition to these, there were the extremely pleasant occasional calls at the Osler house, where many people gathered for tea in the late afternoon. Mrs Osler presided, usually assisted by a niece or one or two other charming young women. Conversation was general until Dr Osler came into the drawing room from his consulting office across the hall. As he entered, there was a wave of his hand, an amusing quip or a gentle tug on the ear for each guest, according to his or her deserts. After a few jokes and a little chatting, he would draw aside an important visitor, a member of his staff or, lacking these, a student, ask a few questions and talk for a little while. Then, unfailingly, he would suddenly draw a gold watch out of his waistcoat pocket, glance at the time, appear horrified that it was so late, plead the excuse of an important engagement and hurry away to a consultation or a committee meeting, leaving the guests to the care of Mrs Osler.

Such intimate and unusual relations as these led to the feeling among his students that Osler was not only the Chief, but also a sympathetic friend, to whom one might turn for advice and assistance when these were most needed. Thus it was that after graduation, when Simon Flexner kindly offered me a post to work under him in the Ayer Clinical Laboratory of the Pennsylvania Hospital in Philadelphia, I told Dr Osler of my good fortune. He immediately volunteered, as was his custom, to write a few letters of introduction for me, and not only did so but told me a good deal about the men that I might be thrown with in Philadelphia. Of one, he said, "He is a good fellow, still young and active" of another, "He is the salt of the earth", of a third, "He is interested in the arteries and knows much about them, but some years ago he crawled up on the bank and has sat there letting the stream run by."

Osler's farewell words to me were, "Remember silence is golden, don't you do the talking, you do the listening and you'll learn much" Needless to say, profit came both from the letters and from the advice

Three years after I arrived at the Pennsylvania Hospital, the following note came from Dr Osler

November 17, 1904

Dear Longcope

I wish if you have any opportunities this winter for studying aneurism cases in young men you would carefully look for that gummosus mesarteritis which Chiari [Chiari] and others have described of late See the last number of the *Verhandl d Deutschen Path Gesellsch* I should like very much to see some good specimens

Sincerely yours

W Osler

Chiari's paper had appeared in 1903, and the subject had already interested us in the laboratory, for we had seen this peculiar form of mesaortitis not only in cases of aneurysm, but also in the walls of the aorta in cases of aortic insufficiency Dr Osler was then preparing his classic article on aneurysm for the fourth volume of his new system of medicine,² and, when he learned that we had several specimens showing the lesions to which he referred, he came up to Philadelphia to spend an afternoon with us in the laboratory Surrounded by residents, as the house officers were called, he sat at the laboratory bench examining one microscopic slide after another, while he discoursed to his small but fascinated audience on aneurysms It was a red letter day for all of us

This was not his only visit to the Pennsylvania Hospital Once he spoke there of forming a club of physicians, similar to one that had been organized by the surgeons A little later, before he left for Oxford, he founded the Interurban Clinical Club The first meeting was held in Baltimore on a Friday and Saturday in April 1905 It proved to be a memorable occasion on account of the demonstrations of heart block, if for no other reason First, Dr Osler discussed the cases of patients with Adams-Stokes syndrome in the wards of the hospital, then Dr Erlanger performed experiments on dogs in the physiology laboratories, with the heart exposed before our eyes, he produced auriculo-ventricular dissociation and complete heart block by clamping the bundle of His The entire performance, from beginning to end, was so brilliant, so complete and so convincing that it was profoundly impressive

It was some years before I saw Osler again³ In the summer of 1907, Dr and Mrs Osler asked Dr Thomas Boggs and me to spend

² Osler, W, and McCrea, T Modern Medicine Its Theory and Practice, vol 4, Philadelphia, Lea & Febiger, 1908

³ The material in the subsequent seven paragraphs originally appeared elsewhere (Longcope, W T Men in Medicine A Visit with the Oslers, *Interne* 11 197 [Sept] 1945)

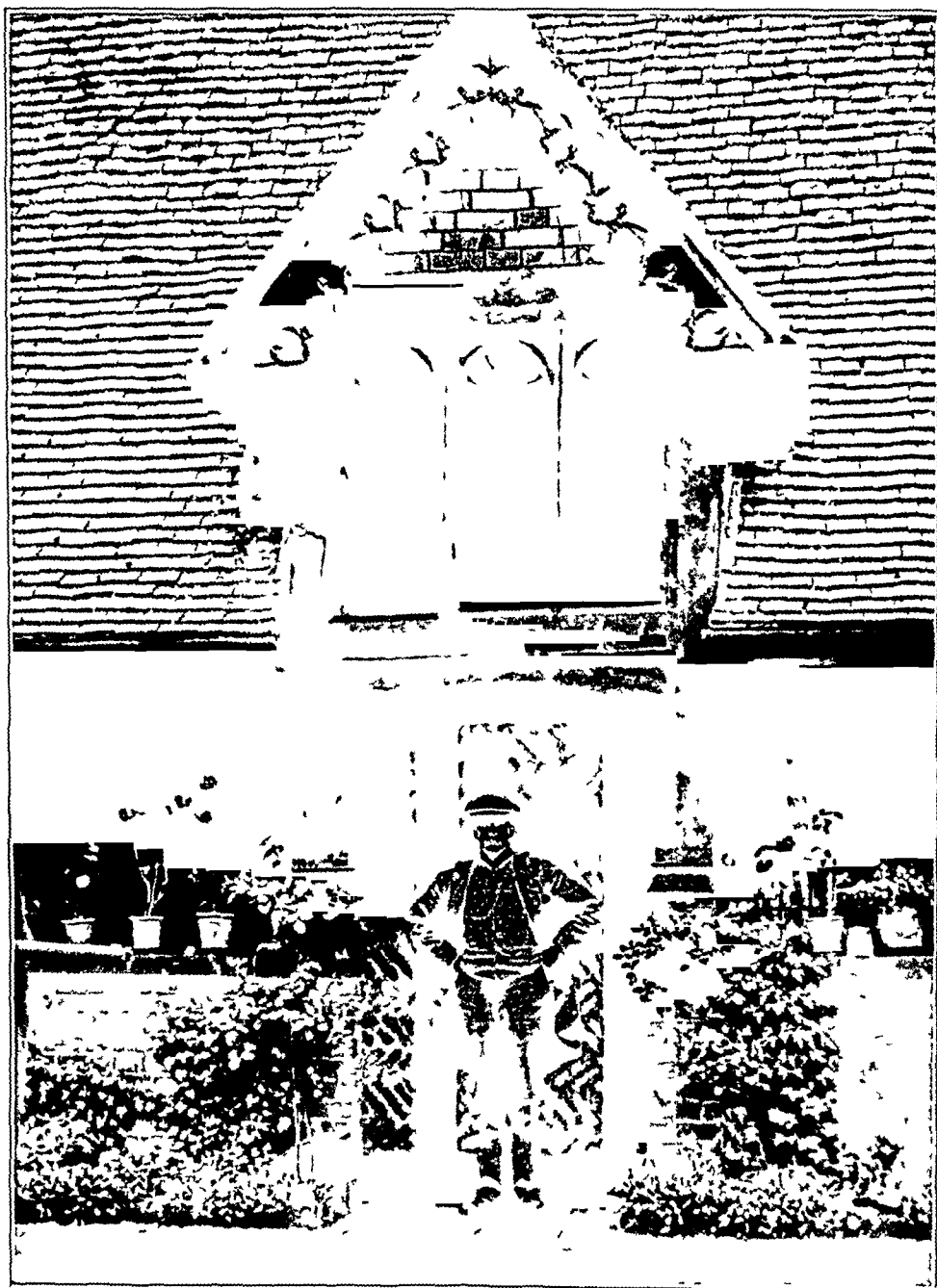
a few days with them at Oxford. We were making a brief tour through a few of the Cathedral towns in the north of England, after a short stay in York and Lincoln, we had reached Peterboro, when Dr Boggs injured his knee and was laid up with a swollen joint. His one desire was to see Dr Osler as soon as he could, so on a fine day in August, we crossed the lovely English countryside in slow trains and, after many changes, arrived in Oxford the same evening, before we were expected.

Nevertheless, Mrs Osler welcomed us, and both she and Dr Osler showed much solicitude over Bogg's painful knee. The Osler's had taken possession of their house at 13 Norham Gardens the winter before and, after making much needed repairs and alterations, were only beginning to feel comfortably settled. We had scarcely stepped inside the door when Mrs Osler pointed to the pipes that rose to the upper floors in the angles of the walls, explaining that the house was so substantially built that all the plumbing for the added bathrooms had to be placed outside, rather than inside, the walls. Their efforts and inconveniences had, however, been amply rewarded, for "The Open Arms," as 13 Norham Gardens had been named, with its large library, its many rooms and its terrace leading to the garden filled with flowers, was altogether charming.

While Dr Boggs was, for a day or two, relegated to the state of an invalid, I was at liberty to follow Dr Osler in some of his many activities. In the morning there was a visit to the Radcliffe Infirmary, where Dr Osler gave advice about one or two patients requiring some special attention, joked with the convalescent patients and then led the way to the clinical laboratory, where he examined some interesting blood smears.

From the hospital, we went at a great pace to the Bodleian Library. This magnificent library was one of his most cherished interests, for he was an ardent student of the classics. On this account, he had been made a Curator of the Bodleian, and a member of the Standing Committee almost as soon as he reached Oxford. These responsibilities gave him much pleasure, he had already instituted changes, suggested additions and obtained extra funds for the purchase of rare books. "A Bodleian Guide for Visitors," prepared by Andrew Clark, Honorary Fellow of Lincoln College, had been published in 1906 at the Clarendon Press in Oxford, and, Dr Osler, as a delegate of the well known press, took great pleasure in putting the little book in the hands of any friend who visited the library with him. Needless to say, my copy has been preserved as a valued memento of the visit.

There was a wonderful morning on the terrace when Dr Osler showed us, among other books, an early edition of an old anatomic work and regaled his little son, Revere, with witty remarks about the quaint woodcuts that illustrated the text. One or two Rhodes



"The Master of Ewelme," standing in the cloisters of the almshouse (1909)
The fifteenth century bargeboards on the gable are unrestored

scholars wandered in, and the conversation turned first on their work and responsibilities, and then on a new society, the Association of Physicians of Great Britain and Ireland. Dr Osler was one of its founders, and indeed largely responsible for its organization. The first

meeting had been held that spring in London, and he spoke with some enthusiasm of the success which had attended it. It had been decided, largely at Dr Osler's suggestion, to start a new medical journal, for which the association would be responsible. It was to be called the *Quarterly Journal of Medicine* and was to be published by the Clarendon Press in Oxford. The first number, containing several carefully selected and important papers, was to appear in October. Dr Osler thought that the association and the new journal would do much to stimulate research in clinical medicine, and was eager for the papers submitted for publication to represent the results of serious studies or original investigations.

There was reference later to Ewelme, the ancient almshouse of which Dr Osler, as Regius Professor of Medicine at Oxford, was master, and the next day we were driven in Osler's new automobile to this picturesque old establishment for a picnic lunch. Only a glimpse of the little church, with its square tower and the adjoining cloisters with their accommodations for thirteen old men, was required to understand the fascination of this unique survival of the Middle Ages. We wandered through the charming cloisters, saw the master's quarters, where the Oslers occasionally spent week ends, and were shown the precious documents which had been discovered in a rusty safe, opened by force. These old manuscripts and parchments dealing with the founding and support of the almshouse, some dating back to the middle of the fifteenth century, were described by Mrs Osler as having been in frightful condition, covered with green and black mold. Dr William Francis had undertaken the delicate job of drying them in the sun, and Dr Osler described the thrill of excitement when it became possible to read these priceless records of the past. They were immediately transported to the Bodleian Library to be put in order and framed. Perhaps nowhere else in the world could one have spent such a day as this, we returned to Oxford feeling that we had really been given a sight of the Middle Ages.

On the afternoon before going up to London, we ambled down with the tea basket to the tiny river Cherwell, which flows past the beautiful tower of Magdalen College to join the Thames. From a little platform we all piled into a punt and were poled up the river, as it meandered through the meadows, until we came to a particularly attractive spot. There, sitting on the grass, Mrs Osler made tea for us, which we drank while consuming enormous quantities of bread and jam. It was a beautiful afternoon. In the distance we could see the towers and spires of Oxford, lit by the declining sun. Revere and his father played together while the rest of us lolled on the sod and chatted. It was so peaceful that there could have been no possible intimation of what was

to come later I wish it were possible to preserve, as the last remembrance of Dr Osler and his family, the quiet charm of this enchanting visit to Oxford But, alas! That cannot be

In March 1917, I received the following note, written by hand

29, III, 17
13 Norham Gardens

Dear Longcope

I fully realize that you must all stay at home and help 'Tis a difficult situation I do not [see] how you can keep out of the row Things are going well here—ships getting through and the outlook better, but the Germans are not beaten yet and I fear we are in for another winter The boy is hard at it on the Ancre in this follow-up movement He keeps well but it must be a hard experience for these young chaps

Love to Janet and the baby Nothing like a baby in the house is there? except two!

Yours ever
Wm Osler

Within a month we were at war, and on August 29, five months to a day after the letter was written, Revere, the only child, "the boy," was killed in action near St Julien

Somewhat over a year later, Dr W S Thayer, then a brigadier general, and I spent a week end at 13 Norham Gardens We had been ordered from the Headquarters of the Medical and Surgical Consultants of the American Expeditionary Force at Neufchateau, France, to London, for a conference on influenza Leaving Le Havre on the night of Nov 10, 1918, we arrived at Waterloo Station in London at 10 50 on the morning of November 11 Suddenly, as we came out of the station, there was a deafening barrage of "archies" (antiaircraft guns) Shrapnel burst high over our heads A woman beside me yelled, "My God! They're coming again!" Then some one shouted, "Armistice! All fighting stops at 11 00 a m!" We looked at our watches, it was exactly 11 o'clock At the same moment there were a shriek of whistles and an exalted ringing of innumerable bells and chimes, and pandemonium was let loose

We got into a small staff car and were driven toward headquarters Crowds filled the streets Women, tears streaming down their cheeks, ran out of shops, shouting and waving flags Our way led past Buckingham Palace, and, as we approached its great iron gates, we saw crowds running in that direction We were surrounded by people, and the chauffeur stopped the car We looked up, and there, standing on the balcony of the Palace, just above us, were the King and Queen The King was in Naval uniform, and beside him was one of the sons, in khaki The crowds below shouted and waved flags There was the sound

of a band, and as it grew louder, we saw the Guard march up and stand at attention beneath the balcony. An officer made an announcement to Their Majesties, and then the band burst forth with the National Anthem. The war was over. The effect was overwhelming. We could only stifle our sobs.

On the afternoon of November 16, we left London, still in a jubilant uproar, and were motored to Oxford by Sir Bertram Dawson, later Lord Dawson. The sudden change from the turbulent streets of London to the quiet of Oxford gave some intimation of what awaited us. When we reached 13 Norham Gardens, we found the house chilly, with most of the rooms closed. Only the library and the dining room were in use downstairs. In the library, Sir William stood in front of the mantel, his back to a miserable little fire in the grate, trying to warm his hands. All the buoyancy and gaiety and the engaging wave of the hand had disappeared. The wonderful Chief had shrunk to a little old gentleman.

The welcome to General Thayer and the smile which he gave us must have cost him dearly, but the inevitable emotional strain which those two devoted friends must have felt was immediately relieved by the entrance of Lady Osler. The entire situation changed, for it had been her superb courage that had supported Sir William through the terrible months following the death of his son, whom he had idolized.

Lady Osler told us later that it was only on the rarest occasions that Sir William could trust himself to speak of Revere, but that evening, as we drove to Christ Church College for one of the monthly dinners, he did talk of Revere and of his plans to donate the "boy's" library to the Johns Hopkins University. Revere had been an enthusiastic fisherman and had accumulated an important collection of books on angling. Perhaps his interest in Izaak Walton had led him to delve further into the literature of that age, at any rate, he had brought together an extensive library of the Tudor and Stuart periods. It was this collection of books, together with Revere's fishing tackle, that Sir William proposed to donate to the Johns Hopkins University, with the idea that it would form the nucleus of a club to encourage the study of English literature of those periods. Founded in memory of Revere, it was to be called the Tudor and Stuart Club. An endowment to accompany the gift would suffice to make appropriate additions to the library. Since its original organization, with Dr. Frank J. Goodnow, president of the Johns Hopkins University, as the first president, the club has flourished. A special room at the university was set aside and attractively altered to house the library and to provide a comfortable place where the members could read, study and meet congenially.

We arrived at Christ Church College to find a small group gathered together for dinner. The evening proved most interesting and in spite of war rations the dinner was excellent. After dinner we sat about a fine old table and drank port, and the conversation was good and lasted long.

The next day after a visit with Sir William to the Radcliffe Infirmary then used as an army hospital we said goodbye with great reluctance and took the train for London.

It was scarcely more than a year later that Sir William Osler died on Dec. 29, 1919. With his death, the entire world was bereft of one of its great figures in clinical medicine.

"Cornhill Farm

HERO WORSHIP

WILDER PENFIELD, M D

MONTREAL, CANADA

ONE HUNDRED years after the birth of William Osler is a fitting time to revive old memories of the master of clinical medicine, and a good time also to bring forward new knowledge of him. During the later years of his life he was a hero to the rising generation of medical men, and after his death biographers heaped his shrine high with tributes, higher than the hero himself would have liked, no doubt. And so, for those who did not know him, I fear this fulsome praise may have obscured the simplicity and the charm of the man.

Some of the material to be presented here may seem sophomoric, but it is new, for contemporary descriptions of Osler by his own students are rare. Perhaps this is because greatness close at hand may pass as commonplace, perhaps it is only that the undergraduate perceives the danger of expressing his opinion of his teachers, at least in public. Even the charming letters of J B MacCallum,¹ written when he was a student at Johns Hopkins (1896-1899), contain only occasional references to the professor of medicine, as in the following examples:

I was called up in Osler's Clinic. They are the nicest things we go to, for Dr Osler sits on the table and swings his feet, and asks you all sorts of questions you have never heard before. Dr Osler's clinics are splendid. It is so nice to hear him talk to the patients. He has a joke for everyone.

And again, when young MacCallum himself was Osler's patient, he wrote:

You can't get anything out of him. He is always talking such a lot of nonsense.

From the unpublished letters of another medical undergraduate, I have culled more extended references to Osler, during his Oxford period. I seem to remember this student well enough, but I hardly

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

A portion of this essay was read before the meeting of the Osler Society of the University of Western Ontario, London, Ontario, Canada, Jan 24, 1941, and the paper was subsequently published (Penfield, W. Sir William Osler, Univ West Ontario M J 11 79-88 [March] 1941).

1 Malloch, A. Short Years. The Life and Letters of John Bruce MacCallum, Chicago, Normandie House, 1938.

realized how naive he was until I came on these letters, written to his mother. The young American had heard a little of Osler's heroic past, so his first reaction was one of surprise to find him an ordinary man, like other men. One week after beginning his medical studies, he wrote, from his rooms in Merton College, Oxford

[January 1915] When I look up at the seven volumes of Osler's *Medicine* on my shelf, it makes me, mentally, worship him. It does not seem possible that he can be the same middle-aged man I saw last Sunday, who, with a room full of guests, spent most of his time in pretending to bandage up the leg of a young officer, to the glee of two little children.

Sir William was a regular kid, but he said to me "Don't you go to the Front, you have got to use all your vacations in real work. I'm going to watch you and see that you don't go home any vacations," so I guess I'm committed to vacations in Edinburgh and will see little work in France.

At the end of the year, in December 1915, the student wrote

Sir William had the students of his department out to his home one evening and he talked very interestingly about the origination of Physical Diagnosis and showed us some of his priceless collection of early manuscripts and writings of doctors, old Latin things, for Latin was the only written language of medicine for a long while.

[January 1916] Davison² just came in and said that Osler had 'phoned him and asked if he and I would not like to go down to Cliveden with him tomorrow, it means cutting one lab, but of course I will go. He goes to Cliveden each week to inspect the big Canadian Hospital there.

And, again, in February

Sir William told the story of his life last night, at a meeting of the American Club, simply, with no affectation nor false modesty. He said he started with every opportunity, seventh in a missionary's family [the student misquoted Sir William, who was the eighth child], with twins ahead. He took time for a "gilt-edged" degree and for working too. When the Hopkins was being built, he was at the University of Pennsylvania Medical School. He said one morning Dr. Billings walked into his room and said "Osler, we are opening the Johns Hopkins in a month, will you go down and take charge of the School of Medicine with Welch?" Osler said "Will I? Yes" "All right, someone will write you, good morning."

When he was in England in 1904, and tired almost to death with the work and engagements of Baltimore, they offered him this job here (the Chair of Regius Professor of Medicine). So he cabled his wife. Her answer was characteristic—it was, "Don't procrastinate, accept at once. Better to leave Baltimore in a ship than in a wooden box." So he accepted.

He said, at the end, that *his rule had been to like and sympathize with everyone*. That's his creed, I think. He is the least sentimental and the most helpful man I've ever seen—the most lovable. You may believe that he is stimulating to me, too, and is on something of a pedestal. If I were not so dumb, I should have the nerve to hope and dream I might follow in his footsteps.

2 Wilburt C. Davison, then Oxford undergraduate, now Dean and organizer of the Faculty of Medicine, Duke University.

On March 24, 1916, while crossing the Channel for a second trip to a Red Cross hospital in France, the student was wounded when his ship was torpedoed. He was returned to a military hospital, in Dover, from which he wrote as follows

This is easily the best ward in the hospital. I am learning lots, lots. Bedside manner, I think I've discovered, is nothing but the effect of the doctor's personality. A young, handsome doctor left me hating him after three minutes of hurried examination. It was not that he did not know, but that he did not care about me, or my feelings.

My! everyone is nice. Both Sir William and Lady Osler and their cousin have written and Sir William telephoned.

[April] Received my first bunch of flowers. The first ever. They came from Lady Osler. I can hardly understand all their kind attention. A letter came from him yesterday to tell me about the surgeon who is in charge of me, Mr. Linington. He says he seems to be a good man, to judge from his directories, and he remembered an article by Linington in the *Lancet* and told me to ask the latter about it. So I did, and he seemed quite pleased and brought it for me to read. This morning, Mr. Linington said he had heard directly from Sir William.

That was his way of helping, from behind the scenes. A month later, it was the student's unbelievably good fortune to find himself in the Osler home at Norham Gardens, where he wrote on Easter morning.

It is good to be so near Sir William. He does not dislike anyone. He sees good and something to admire in everyone, and I've seen his face cloud up when someone repeated a bit of scandal or criticism. He is full of vigor and energy.

Last night he came into my room about 10 o'clock, as he has each night, in the red smoking jacket. I showed him an X-ray photograph and simple photograph of one of my ten cases at Ris Orangis, which Dr. Blake [Dr. Joseph Blake, then chief surgeon of Hospital Militaire V R 76, now a surgeon in New York] had operated on. He said it was unique, and advised me to publish it!

Breakfast comes to me in bed. He forbids my getting up before. The silver and the little portions seem good after Dover. Soon Revere and Sir William both come in to see what they can do. Revere is a captain in the R A M C but is home on leave waiting his change into the artillery. After I am dressed, Lady Osler comes in to talk a little. Never before have I been waited on like this. If I enter a room, Lady Osler gets me a pillow, and someone else a footstool, etc., until I sit down quickly in a sort of shame.

Much of the nice days I spend on the terrace overlooking the garden and Oxford Parks. I never heard such birds as here in England. It is like a great choir, the quality of whose voices is ever changing. I read Physiology, or, perhaps, one of the books Sir William has brought me, on the endocrine organs. One of them is in Italian, a great tome, but I look at the pictures and puzzle out a few words.

Two little kiddies came in to see "William," as they call Sir William, the other day and, to amuse them, he took them up to a second storey porch which overlooks the garden, and from there he threw water down on Lytle and Davison, who had come to see me. Then, when Lytle put up a lady's umbrella, which lay there, he poured a whole pitcher of water full on him, while the kiddies screamed with delight.

After this two weeks' idyll, the student moved back into his Oxford lodgings, but the kindness that emanated from the Osler household did not cease. Revere Osler once came in after a day's fishing on the Thames and left a trout for him. In a short time he wrote

Let me tell you what Sir William has done now. He had Davison and me to tea Thursday afternoon, and then we went down to his office in the Museum. Here was a great collection of medical books and of his own reprints. The books were about to be sent to the University of Louvain. "Now," he said, "you boys had better take what books you like here, about 20 apiece, and take a set of reprints," and he went off with his springy step, waving his hand as he slammed the door to cut off our attempted thanks. We took off our coats and dove in, carrying off 40 and, later, splitting them in my room. I have a dandy two-volume surgery, etc. etc. But the reprints are the best of all. You've no idea what that man has written on—almost every topic in medicine. And now he tells us to bring the reprints to tea this afternoon, and he will send them away to have each set bound and titled.

I shall never do it, but I'd like to get a first class in the final examinations because of what Sir William will think.

In these youthful letters there is nothing very extraordinary, but they tell one why every medical man and student who knew him loved him and resolved to emulate him. Osler was a simple man, who never made his juniors conscious of the fact that they were in the presence of greatness. What is more important, I think that he himself never gave a thought to the length of his own shadow. He had too lively a sense of humor for that, and, besides, he was much too busy following his own rule of life "to like and sympathize with everyone."

In the summer of 1917 the medical student had found his way to Paris. There he received a letter from Lady Osler:

You will, I know, grieve for us when you hear that Revere died August 30th from wounds. It is too horrible to take in, and yet we expected it. I prayed Sir William might be spared this. We know little yet. The first news came from Major Harvey Cushing, who was with him at the C C S, and that comforts us so much. I am bothering you—by asking you to do this for me—but know you will not mind. So many of Sir William's friends are in France, and I know all will have the New York Herald (Paris edition), and so I am asking you to put this among the death notices.

"Died of wounds received in Belgium, Edward Revere Osler, 2nd Lieut, Royal Field Artillery, aged 21. Son of Sir William Osler, Bt, Regius Professor of Medicine at Oxford, and of Lady Osler."

That the death of his only child and dear comrade was the greatest sorrow that life brought to Sir William seems obvious. But, although his nights were passed in agony, that house, which had gained the name of "The Open Arms," an asylum which had continuously shut its guests away from the worries and cares of wartime, did not now become a place of lamentation.

The week end after the receipt of the news of Revere's death has been described by Dr Robert Osgood, of Boston. When he heard the news, he immediately proposed to recall his acceptance of an invitation to visit Oxford, but he was informed that both Sir William and Lady Osler would be "distressed and almost displeased" if he did not come. Therefore, with misgivings, Dr Osgood carried on with the visit, which he described as follows:

Sir William met me on the Oxford platform, gay, debonair, with a flower in his button-hole, and, as we drove to Norham Gardens, was as scintillating, humorous and charming as he possibly could be, without a suggestion of any lurking sadness.

Soon we dressed for dinner, at which there were perhaps half a dozen guests who were spending the week-end, including a scholar, whose name I have forgotten, connected with the British Museum, a Canadian lieutenant, who was just having his leave from his regiment in London, and myself. It was a very merry dinner party, and Lady Osler seemed as completely in control of herself and her emotions as did Sir William.

After dinner, when the gentlemen had gone upstairs to smoke in Sir William's library, he would pull down a non-medical book from his shelves and ask the scholar from the Museum something about it and his opinion concerning it, and it would be quite evident in a few minutes that Sir William was very much the more conversant with this non-medical book. He would then touch on some medical subject and address me, and I would, of course, scuttle as gracefully as I could beneath his feet. He would then turn to the Canadian lieutenant and discuss with him the size of Gertie Miller's ankles (she was then the leading vaudeville star) and he had considerably more knowledge of their size and pulchritude than the young lieutenant.

So the evening went. With the ladies he was again, of course, the brilliant leader of conversation.

That night Dr Osgood slept little, at dawn, before others were stirring, he dressed and left his room to go for a walk in the Parks. As he passed on tiptoe down the hall he was startled to see, through the crack of a slightly opened door, Sir William, kneeling in silence by his bed.

Sunday, Lady Osler went to church. There was another very considerable party at luncheon. In the afternoon twenty-five American aviators were in for tea with gaiety unconfined.

It was almost more than one could bear, this apparent gaiety, this complete obscuration of his real feelings, because it was war-time and the sporting thing to do. Lady Osler entirely caught his spirit and talked and acted in complete harmony with his mood. I fancy efforts like this may have lost him to the world too early.

Aequanimitas! That was the word he had placed on his own crest when he was created a baronet. *Aequanimitas* was an essential quality in his character. He did not strain to do more than he could, but took all things in his stride—even the death of Revere.

Sir William Osler devoted his mind to medical education, to the study of clinical problems and to the lore of medical history. In all those fields he was a distinguished leader, and yet it is not altogether because of these qualities of the intellect that Osler Societies have sprung up in so many parts of the English-speaking world, chiefly composed of students or of young physicians. The unique quality of this man had to do with the "heart."

I would have you see him, through the eyes of the previously quoted undergraduate, as "the least sentimental, the most helpful, most lovable," teacher of medicine. He belongs to medical students of all time, as Lincoln belongs to common men everywhere, a man who grew to be what he was by dint of hard work, and in whose footsteps any undergraduate may dare to "hope and dream" that he may follow.

SIR WILLIAM OSLER REMINISCENCES

WILBURT C. DAVISON, M.D.

DURHAM, N. C.

“IT ISN'T done,” a reply, which is supposed to end all arguments at Oxford, was the only answer I could obtain in 1913 when I wanted to complete the first two years of the medical school in one year. However I was not convinced that it could not be done, so as a last resort I was told to call on Sir William Osler, the Regius Professor of Medicine and dean of the medical school, who had lived in the States and would know how to handle an argumentative American student who did not understand Oxford traditions.

An appointment was made and I rang the bell at 13 Northam Gardens, Sir William's home, with fear and trembling because to me and most Americans the name, Osler, was the pinnacle of medicine. By that time I profoundly regretted even considering my proposed crowded schedule but as the appointment had been made I had to make the call. When the door opened I had decided to withdraw my request, to apologize for my temerity and to retreat in haste. However I was delightfully surprised when a small man came to the door and said cheerily before I could open my mouth, “I am Sir William and have heard of your request which I think is very foolish but of course you can do anything you please and now let's have tea.” Taking the amazed me by the arm he propelled me into the drawing room introducing me to Lady Osler with, “Grace, here is a new American colt who is wrecking a medical school tradition, give him some tea.” Both of them were so charming and friendly that I soon felt I had two friends at Oxford. My awe immediately turned to adoration and devotion. This extremely pleasant and informal reception instead of the terrifying one I had expected was the first of many delightful memories I shall always cherish.

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Delivered at the Osler Society of McGill University, 28 March, 1947, on the 75th Anniversary of Osler's graduation. July 12, 1949, will be the one hundredth anniversary of his birth.

From the Department of Pediatrics, Duke University School of Medicine and Duke Hospital, Durham, N. C. Based on memories of student days at Oxford, 1913 to 1916.

of the Oslers Sir William never mentioned the two-year-in-one medical school schedule again, but I soon found that though I could and did attend all of the courses, my knowledge of their content remained very meagre I had exceeded the limit beyond which medical education could be accelerated

It was Sir William's custom to dash into various laboratories and to ask amusing and often disconcerting anatomical questions of students who were dissecting or to look down the microscopes and inspect the slides of those studying pathology and bacteriology Osler was a magnificent teacher and made everyone with whom he came in contact feel that he was primarily and genuinely interested in that individual I have since met hundreds of his former students in America and England who shared that belief For example, Thomas B. Fitcher, who was supposed to give me an examination in medicine when I transferred to the Hopkins in 1916, happily chatted about the Chief for an hour and then gave me a good grade John Musser did the same thing when I took the National Board in 1919 In fact passing examinations seemed more dependent on knowing Osler than on a knowledge of medicine—perhaps they are synonymous

During my first year I attended his ward rounds every week at the Radcliffe Infirmary and although I had great difficulty in understanding many of the medical terms and still more in spelling them I was occasionally delegated to write on the histories the notes he dictated I may not have learned much clinical medicine at this stage but I believe my preclinical work profited tremendously for it was made more interesting because its clinical application and significance were made so apparent By attending Osler's ward rounds while a first year student I was unconsciously performing an experiment in medical education which is now part of the curriculum in several medical schools

One of the most delightful features of the medical training at Oxford was Sir William's interest in the history of medicine At intervals throughout the year he would send six or seven of us one of the following treasured invitations

From the Regius Professor of Medicine, Oxford

Dear Davison,

If free dine here please with me Thursday evening, 23rd 7.30

Sincerely yours,

Wm OSLER

After dinner he would bring out many of his precious books and we would spend hours in poring over them while he explained the part Avicenna, Paracelsus, Leonardo da Vinci and others had played in

medicine These evenings gave us a background that was invaluable This pleasant indoctrination gave me a leading interest in medical history, culminating in visits to the Aesculapium at Epidaurus and other medical shrines

Just before the long vacations at Christmas, Easter and during the summer he would ask us our destinations and then supply us with cards of introduction to the leaders of medicine at these various centers In no other way could we have obtained such facilities for study in London, Edinburgh, Dublin, Paris and Germany On one of these trips, he had told me to be sure to go to what I thought must be a Paris night club as I had written the word "Sore-bun" in my notebook I soon learned that he had been talking about the Sorbonne, the center of French intellectual activity

These letters of introduction were an open sesame for Sir William had friends everywhere who delighted to help anyone he sent For example, on learning that Wilder Penfield, a fellow medical Rhodes Scholar, and I were going to London, Osler suggested that we attend Sir Arbuthnot Lane's clinic at Guy's Hospital and gave us a note to him We arrived after Sir Arbuthnot had started operating so we donned white gowns and masks and were given seats in the operating room Lane was applying his steel plates to a patient's broken leg and making very rude remarks about Americans in general and Dr Fred Albee in particular We gathered from Lane's complaints that Dr Albee, on the preceding day at the Royal Society of Medicine, had said his bone grafts were superior to Lane's steel plates which acted as foreign bodies and would bend After he had finished he pointed to me and said, "You look strong, just try and bend one of my plates" Naturally I had been annoyed by Lane's diatribe against my country so I did my best to bend his plate and succeeded After all I had been rowing for six years and had fairly strong hands and shoulders Sir Arbuthnot's astonished face as I handed him the bent plate was purple He called his assistant and bawled him out for not having the plate properly tempered When we handed him Osler's note, Sir Arbuthnot's belligerent manner immediately changed He spent the rest of the afternoon with Penfield and me trying to atone for his rudeness, took us all over Guy's Hospital, and even drove us to the American Embassy in his car

On another occasion while I was obtaining training in obstetrics, or midwifery as it is called in England, at the Rotunda Hospital in Dublin, Sir William gave me letters of introduction to Sir John Moore, the professor of medicine, and Sir William Smiley, the professor of midwifery, who could not have been kinder to their own relatives The former took me sight-seeing—showing me the ancient books in Trinity College, even climbing up to the organ loft of St Patrick's Cathedral with

me, and then saw me off at the station. The Irish are delightful people, though they woke me up every morning drilling in the street under my window in preparation for the Easter rebellion in 1916. I delivered thirty-five babies in the hospital and district and decided that though obstetrics was a necessary specialty I would rather do something else. However it was a grand experience.

Research in England is much more difficult than in this country because the British antivivisectionists had persuaded Parliament to pass very strict laws about animals. Perhaps one of the reasons that the United States and Canada are now leading in medicine is because we have been able to restrain our misguided ignorant obstructionists. However in spite of the legal restrictions, Osler, Georges Dreyer, professor of pathology, and Sir Charles Sherrington, professor of physiology, constantly stimulated their students to undertake research problems. As a result of their enthusiasm I wanted to do research, and Sherrington offered me a laboratory with my own key—a notable event—so that I could study the effect of intravenous fat on recovery from anesthesia. In order that I could do this and other research work, Sherrington and Sir Frederick Taylor, president of the Royal College of Surgeons, had to apply to the British Home Office for a certificate for me. After I had obtained my certificate Sir John, [later] Viscount, Simon, “one of his Majesty’s principal secretaries of state,” issued me a licence—English spelling. The experiments didn’t prove anything but the experience of working with Sir Charles was invaluable.

Osler and Dreyer were anxious to prove the efficacy of triple typhoid-paratyphoid vaccine in order to protect the British Army against the numerous paratyphoid infections in the Dardanelles and Mesopotamia, as well as in France, so under [the guidance of Dreyer, E. W. Aimley Walker and A. Duncan Gardner (who at the time of writing occupies Osler’s chair as the Regius Professor of Medicine at Oxford)] I inoculated some of the medical students and a number of rabbits with triple vaccines and others with straight typhoid and paratyphoid vaccines, and tested their immunity by agglutination tests. The results justified the adoption of the vaccine. Osler then asked me to write a paper on Dreyer’s methods for the *Journal of the American Medical Association*, my first publication. And after I returned to the States I was requested to write a report on it for the National Research Council as the American Army was considering the adoption of triple vaccine.

Sir William worked like a Trojan during the war and helped in every way possible the advances in war medicine. He summarized them: “Science has made great advances in the more prompt care of the wounded, in the treatment of wounds, better surgical technique, the lessened time of convalescence, the whole organization of nursing and in

the practical stamping out of disease by preventive inoculation" He was particularly interested in typhoid and paratyphoid The shortage of nurses and orderlies on the hospital ships from the Dardanelles was a great difficulty Sometimes bedpans were passed from one patient to the other until they were filled As a result some of the patients caught each other's infections and the cases were difficult to diagnose when they arrived in England Osler was very anxious to study these mixed infections with Dreyer's technique and I applied with his help for assignment to the Aquitania [one of the hospital ships] However the Admiralty did not want any Americans in the Dardanelles campaign

While carrying out the experiments with triple vaccine after my return from France and Serbia in 1915, I learned that the Radcliffe Infirmary, the 200-bed hospital in Oxford, needed an intern so I applied and because of the shortage of physicians I was appointed although only a third-year medical student The work was fascinating and there was plenty of it for the hospital had only three on the resident staff—Mr MacDonald, the resident surgeon, Dr Mosse, the resident physician, with me as casualty house officer, which means man of all work I took the patients' histories, gave anesthetics, assisted at operations, and, best of all, wrote the notes dictated by Osler, and other members of the visiting staff

Sir William, in addition to being the Regius Professor of Medicine, was the physician-in-chief of the Radcliffe Infirmary, or the Chief, as he had been called in Baltimore before coming to Oxford We always affectionately referred to him as Father William He visited the Radcliffe Infirmary daily except Mondays and Fridays I greatly enjoyed these ward rounds for his comments on the patients always were amusing as well as instructive The patients adored him Cases which seemed very complicated were soon simplified after a consultation with him Osler was at his best on the wards He spent much of his time on the children's ward and my interest in pediatrics probably started there, although I was not conscious of it until I met John Howland the following year In spite of his skill in physical diagnosis, Osler was one of the leaders in advocating the use of roentgenograms When a visiting professor from Harvard claimed that percussion was as accurate as x-rays in the determination of heart size Osler proved him wrong which greatly pleased me, as I had little faith in the results of my own percussion

On Mondays, Osler who was a Lt Colonel in the Canadian Army Medical Corps visited the Duchess of Connaught Hospital on the Astor estate at Cliveden As he needed someone to take his notes and collect blood specimens for study he took me along Needless to say I enjoyed the forty mile automobile trips with the Chief although Lady Osler soon labelled me "Jonah" because of the frequent breakdowns of the car Sir William would start the Cliveden journeys by stacking ten or fifteen

medical journals which had arrived during the preceding week on the car seat between us and would read one after another, "dog-eating" the articles which he recommended my reading. He could read and digest medical literature more rapidly than anyone I have ever met, at the end of the two hour ride he would have completed a survey of all of the journals. It took me the rest of the week to cover the articles he had suggested, but it started a life-long habit of reading medical journals for at least a half hour daily. The hospital at Cliveden was Canadian—both the staff and the patients—and was exceedingly well run. Mrs., later Lady, Astor took a great interest in it and usually had us for lunch on our trips. The Canadian staff who like me worshipped Osler assumed that I must know something because I always accompanied the Chief. Although I explained the only reason for my presence was that he had no one else available they would ask me innumerable questions which I could not answer, but I usually would get the information for them from Osler on the return trip.

On Fridays Sir William visited Mount Vernon, the army heart hospital at Hampstead, London, and often took me with him. His ward rounds there with Sir Thomas Lewis were fascinating. As a result I have been interested in heart disease ever since. He also took me to several medical meetings in London, and made me realize that they are the mainstay of a physician's continuous education.

Sunday was Osler's busiest day. He held "grand rounds" at the Radcliffe Infirmary from ten until one. They were attended by twenty to thirty physicians from the surrounding counties as well as by any American doctors who were visiting England. If there were any of the latter—there usually were for Osler made Oxford the Mecca of American medicine—they were invited to lunch at "The Open Arms" as the Oslers called their home. The Chief generally included me in the invitation because he knew that I realized that he needed a nap in the afternoon and that I would always volunteer to show the visitors around Oxford as soon as lunch was over. The Open Arms more than lived up to its name during Sunday tea. Many visitors presented letters of introduction and each one received the same gracious welcome. Even one Fabian student who demanded of the Chief whether he preferred to be called Sir William or just plain Dr. Osler was put at ease by being told "just plain Dr. Osler." On another occasion I heard the same question asked by an individual whose very loud voice was making general conversation difficult. Sir William's quotation from Alice in Wonderland, "I answer to his or any loud cry" was so gently and amusingly given that the questioner did not feel rebuked and yet profited sufficiently to lower his voice for the benefit of the others present. After tea Lady Osler would somehow arrange for Sir William to disappear so quietly that no one knew he had gone. It was the only way he could keep up

his correspondence and literary work as he had no secretary during the war and wrote everything in long hand. It was marvelous to see the amount of work he could accomplish—he never wasted a minute. Long conversations and long letters always irked him. On one occasion he wrote across a multi-page letter from a patient “Please return summarized.” It was a good lesson for me—I now rarely write a letter of more than a page.

Even though his contacts with visitors often were brief he never forgot them. For example while Atala Scudder, my fiancée, was at Oxford in 1914 she and I lunched and had tea with the Oslers. Sir William immediately named her Light of my Life and would always mention her in his letters to me, as in the following note I received in France.

27 x 17

13 Norham Gardens

Oxford

Dear Davison,

This has been returned today. I suppose wrong address. All well. Very busy. Americans are pouring thro' & we catch a glimpse of a few old friends. 250 here in flying corps. We have 30 each Sunday for tea. Love to the L. of your L.

Yours,
W O

One day in August 1915 he telephoned me that he had just received a letter from Howard Beal, chief surgeon of the American Women's War Hospital at Paignton, stating that a convoy of jaundiced soldiers had just arrived from Egypt. A letter like that whetted Osler's medical appetite and excited his scientific curiosity. He was sure the patients had infectious jaundice, or Weil's disease, and telegraphed Beal that he was sending me to study them. He gave me F M Sandwith's *Medical Diseases of Egypt* which contained an article on infectious jaundice, and I collected a supply of material for blood cultures and a bacteriological textbook and started for Paignton. I was sure that Dr Beal would be annoyed at having to meet and make arrangements for a third year medical student, so in order that I might at least know something about jaundice and not be a total disgrace I diligently studied Sandwith's article during the long train journey until I could recite it word for word. Fifty patients were ready for inspection when I arrived. All of them had passed the acute stage and were no longer jaundiced but by asking them about the various symptoms and signs that Sandwith had described I was able to confirm Sir William's original diagnosis and also to hide my ignorance temporarily. In accordance with my instructions

I made as many blood cultures as possible but all except one were negative. That culture contained *Staphylococcus albus* which even I knew was a contamination and not the cause of infectious jaundice, or Weil's Disease,—the etiological agent of Weil's disease, *Leptospira icterohaemorrhagica*, was discovered a year later in Japan, and the experience in the North African campaign of World War II indicated that infectious jaundice or hepatitis was different from Weil's disease and was caused by a filterable virus. Sir William came to Paignton a few days after my arrival and was as disappointed as I had been that there were no acute cases to study for he was tremendously keen to find the cause of the disease.

Sir William's interest in his students did not cease after they had gone down from Oxford. Even though without a secretary he would frequently write to us encouraging us in any work we were doing and giving us advice and suggestions.* He knew medicine from Hippocrates to the latest innovation and made his associates want to emulate him.

Osler's creed was to like and sympathize with everyone and not dislike anyone. He saw good and something to admire in everyone, his face would cloud up when someone repeated a bit of scandal or criticism. Aequanimitas was the watchword he himself took with him through his life and he had it placed on his crest when he was created a baronet. He practised tolerance, which is greatly needed in medicine, and admonished his students as follows: "No sin will so easily beset you as uncharitableness toward your brother practitioner. So strong is the personal element in the practice of medicine and so many are the wagging tongues in every parish that evil-speaking, lying and slandering find a shining mark in the lapses and mistakes which are inevitable in our work." We all tried to follow him, but we had to make a conscious effort, while Osler, to quote a popular song, did "what comes naturally." Wilder Penfield's stock admonition to me when I said something disagreeable was "Sir William would not have done that."

One of the examples of his many kindnesses to his students occurred on March 25, 1916, when he heard that Penfield had been injured in the torpedoing of the Channel steamer, *Sussex*. He immediately tele-

*Typical letter

From the Regius Professor of Medicine, Oxford

9, January, 1915

Dear Davison,

So glad to hear from you and I am sure you must be having splendid experience. Do keep some careful notes of your cases, as they will be of value.

My love to Manyon and greetings to Dr. Blake

Sincerely yours,
WM OSLER

phoned the Dover Military Hospital to make arrangements for Penfield to be brought to 13 Norham Gardens. Penfield's leg was badly shattered and after preliminary care at Dover he was brought to Oxford where the Oslers nursed him back to activity.

Another instance occurred in the spring of 1918 while I was in the AEF. Osler wrote that Robert Emmons, an American medical student who had been at Oxford with me, had tried to join the American, British and French armies but was always rejected for varicose veins and other physical defects. Sir William asked me to examine and pass him if my conscience would allow. Needless to say I regarded the letter as an order and was fortunate to have Emmons assigned as an enlisted man in our laboratory. We gave him a room in our apartment but I was soon reprimanded for the army had rigid regulations about the separation of officers and enlisted men.

Osler also could be stern if necessary. Though he never gave direct orders he expected to have his suggestions followed. For example one of his patients had purpura. He suggested that a blood platelet count would be interesting. I looked up the subject and found conflicting evidence on platelet counts so I did not do one. The next day he asked about the platelet count, and I foolishly said that according to the most recent books it was of little value. After ward rounds Osler quietly took me to the laboratory and showed me how to do a platelet count. Osler sincerely believed his dictum that "the master word of medicine is work." I later learned that he had described blood platelets in 1873, and that counting them in purpura as well as in other conditions was very helpful.

Sir William gave me another well deserved reprimand when I delayed accepting a Senior Demyship at Magdalen, because I was waiting to hear from my application for a Beit Fellowship which carried a higher stipend. He quietly but firmly made me realize the embarrassment I had caused to those who had obtained the Demyship for me.

Sir William informally and humorously told the history of his life at a meeting of the American Club at Oxford on February 12, 1916. "Born eighth in a missionary's family with twins ahead on July 12, 1849, in Bond Head, Ontario, then the backwoods, I did not have an auspicious financial outlook. However in 1867 at the age of eighteen years I went to Trinity College, Toronto, with the expectation of entering the ministry. After a few trimesters of the classics I decided that science was preferable for I had always been interested in it. (One of his old friends once related that as a boy he would hunt for animalcula in the horse trough near his home.) I then in 1868 commenced the study of medicine at Trinity but finally decided in 1870 to go to McGill University Medical School in Montreal as the advantages there appeared greater. McGill at that time was conducted along the lines of the Scotch medical schools. At the end of the course a thesis on some subject was

required from every applicant for the M D degree There were two ways in which this could be done, either by paying \$25 to an old physician in Montreal who would perform the task or by grinding it out alone For various reasons I did the latter I spent the summer of 1871 performing autopsies and collecting the interesting specimens When the medical school opened in the autumn my thesis and array of pathological material were ready My specimens were displayed to the faculty in the amphitheatre The summer had been exceedingly warm and the methods for preserving material were not of the best My collection was impressive in more ways than one The professors were so overcome by the sight and smell of my labors that I was awarded a special prize The latter together with financial help from my brother enabled me to go abroad for further study

"After a short tour through Scotland and England I settled in London in Sir John Burdon Sanderson's laboratory to investigate the effects of two drugs on leukocytes This research at least gave me more than a passing acquaintance with the white blood corpuscles and blood platelets I then swung around the grand circuit stopping at Paris and Vienna and ending in Berlin where I met Virchow who made a great impression upon me I had intended returning to Paris but funds were running low so I left for Montreal in 1874 to receive an appointment as instructor in the institutes of medicine at McGill In those days that course meant physiology and pathology Students paid fees directly to the instructors who provided equipment and material and lived on the balance I did more of the former and less of the latter The supply of microscopes was meager and after remedying this defect there was little left in my pockets I had to lecture on physiology which was a stupendous task for me as my medical education had been 'gold plated on a brown stone foundation' However in Germany I had heard excellent lectures and these were being published monthly I would wait eagerly for the mails, then carefully translate the lecture and deliver it the next day I was always haunted by the fear that the supply or the mail would fail me but neither did

"After ten years—in 1884—I had recovered sufficient means to return to Europe Virchow had always been interested in anthropology so my offering to him was a perfect skull of a North American Indian which delighted him I was resting in Leipzig when I received a cable from friends in Philadelphia stating that if I would accept a professorship there I should communicate with Weir Mitchell who was in Europe and who had been empowered to arrange the details I sat up late into the night balancing the pros and cons of Montreal and Philadelphia In the former I had many friends, I loved the work and the opportunity was great In the latter the field appeared very attractive but it meant leaving many dear friends I finally

gave it up as insoluble and decided to leave it to chance. I flipped a four mark silver piece into the air. 'Heads I go to Philadelphia, tails I remain at Montreal.' It fell heads. I went to the telegraph office and wrote the telegram to Dr. Mitchell offering to go to Philadelphia but when I reached in my pockets for money to pay for the wire I found them empty. My only change had been the four mark piece which I had left as it had fallen on my table. It seemed like an act of providence directing me to remain in Montreal. I half decided to follow the cue but I concluded that as I had left the decision to chance I ought to abide by the turn of the coin so I returned to my hotel for it and sent the telegram. It was hard to leave Montreal but I became very happy in Philadelphia where I met Mrs. Samuel Gross, now Lady Osler.

"Five years later—in 1889—I had heard of the new hospital and medical school to be opened in Baltimore so when John Billings who was organizing the new institution entered my room I instinctively knew his mission and accepted as soon as he had invited me to head the new medical service at the Johns Hopkins Hospital. This meant a new severance of ties that had grown up in Philadelphia but as I had survived the transplantation from Montreal I knew that the wounds of this new change would heal.

"After fifteen years of work and happiness in Baltimore during which I wrote my *Principles and Practice of Medicine*—the first edition was in 1892—I was called to Oxford as Regius Professor of Medicine.

This was my third and I hope my last change. Each time I have met new friends and retained the old. At the commemoration exercises in 1905 before my departure from Baltimore I created a furor that was entirely unexpected. I had been reading Anthony Trollope's *Fixed Period* and had been thinking of some professors who had remained at their posts after their period of usefulness was over. It was for them that I with humorous intent advocated chloroform as a peaceful means of retirement. The newspapers made much of it and misquoted it. Boys, do not read Trollope. He is dangerous."

Osler was unjustly criticized for this farewell address at the Hopkins in 1905 in which he spoke of "the comparative uselessness of men above forty years of age." He was not however responsible for the statement that those above sixty should be chloroformed—no one could have been more sympathetically and kindly interested in the aged than Osler—and the reference, as pointed out above, was merely a quotation from Anthony Trollope's novel *The Fixed Period*. In answer to this storm he said: "The criticisms have not shaken my convictions that the telling work of the world has been done and is done by men under forty years of age. The exceptions which have been given only illustrate the rule. It would be to the general good if men at sixty

were retired from active work. We should miss the energies of some young-old men but on the whole it would be of greater service to the sexagenarii themselves." As a matter of fact Osler was one of the exceptions for he was just under forty years of age when he went to the Hopkins and his most productive period was the next ten years. However, most of us are like me, with little productive research after the age of forty, and with a desire to retire at sixty. Dr W. G. MacCallum expressed the same idea in describing the four stages of a medical school teacher—working hard for twenty years for scientific recognition, receiving an appointment as a professor, having a new laboratory or hospital built for him, and spending the rest of his life showing visitors through the new building.

By the summer of 1916 it was obvious that America would soon enter the War so Osler suggested that I return to the States to get my medical degree. It would have taken too long in England, so he wrote to Dr J. Whitridge Williams, the Hopkins dean, to admit me to the senior class. It was hard to leave Oxford. Although I was working seven days a week from six in the morning to midnight I loved the place and my associates. The most difficult part was leaving the Oslers to whom I was devoted. Just before I sailed Sir William called Penfield and me into his study and told us that when he was a young man old Dr Bowditch of Boston had told him that the regret of his life was that he had not saved reprints of everything he had written. Osler said he was now as old as Bowditch and had saved reprints of all of his writings, but the regret of his life was that he had written so much. He invited us to select copies of all of his reprints and then had them bound in three volumes for us. These books are Penfield's and my most cherished possessions.

When Penfield and I returned from Oxford, we roomed together in one of the white-stooped old dirty houses on North Broadway.

We had to have all our records signed by the Hopkins faculty. They all were, but I inadvertently annoyed one of the professors. When he saw Osler's signature on my records he said it was extraordinary how many famous medical men were preacher's sons. He mentioned Osler, Finney and himself as examples but didn't think it funny when I said my father also was a preacher. At first, the Hopkins medical school was a disappointment. After being responsible for a hundred patients in addition to research work and teaching it was a bore to have only six patients on whom to take histories and do blood counts. It took me two months to realize that I was learning more by doing many things for a few patients than I did by trying merely to cover the necessities for a large number.

Pediatric clinics by John Howland soon reconciled me to the Hopkins. After the second one I decided to become a pediatrician,

although Osler had urged me to go into preventive medicine as it had the brightest future of all the medical fields Osler even wrote Dr William H Welch to take me into the new Hopkins School of Hygiene after the war However, I continued in pediatrics, but Sir William's letter to Dr Welch was responsible for my appointment at Duke, for it was Dr Welch who recommended me for the position As a matter of fact, pediatrics through natural evolution has now become a branch of preventive medicine so I followed Osler's advice though I didn't realize it for twenty years

On April 6, 1917, when we declared war, I called on [Col, later Gen] R E Noble, the personnel officer in the Surgeon General's office, and applied for a commission Col Noble said that I lacked two months of being graduated but that if Dr Welch would 'phone him that I could be graduated early he would give me a commission Dr Welch did, saying that as I was not doing very much class work the sooner I entered the Army the better and that my diploma would be sent to me later I didn't receive it until I had been in France several months Col Noble said he would send me a commission within a few days When it arrived I was attached to Army Laboratory No 1 for early overseas duty

I had been trying for several months to persuade Atala Scudder to marry me and she finally agreed, probably against her better judgement I have been very happy ever since and I hope she has One of the best wedding presents was the following letter from Lady Osler

July, 1917
13, Norham Gardens,
Oxford

Dear Mr Jonah

I am perfectly delighted to hear you are married and I wish you both every possible joy Of course we will know at once when you reach England and you must bring your wife to us for a week-end Isn't it splendid that America has come in? We have been very busy lately with all the units that have come over and of course the men dash down to see their "Chief" Revere is in Belgium in the midst of this awful offensive that is just coming off and one is worried to death The motor is still going to Cliveden and *no more accidents* Mr Macdonald & Dr Mosse are going to Egypt They are having the R A M C training now

With all good wishes believe me,

Cordially,
Grace R Osler

On July 12, 1917, I was ordered to France and when I reported in New York I was told that we were to sail the next day on the *Philadelphia*. There was little secrecy about sailing in the early days. I went to the steamship office to inquire whether my wife could go with us. Fortunately the clerk was a romantic soul, and when he learned that we had just been married he gave us the bridal suite on the ship. I had hoped that I might see the Oslers while we crossed England but we arrived in Southampton late at night and had to cross the channel early the next morning. However I was able to talk to them over the 'phone that night. A few days later in France I received the following characteristic cheery Oslerian letter:

Dear Davison,

We were so disappointed not to see you. Congratulations on the Alvarenga prize. So glad. That is a good bit of work. Let me know if there is any literature I can send. The R S¹ in Wimpole St has arranged to send books & papers. So glad that the L of your L² came over. Revere keeps well—says he cannot even get P U O³ after 4 days & nights of soaking wet in the last offensive. Dreyer is away. Ainley Walker lost his wife the other day—an obscure complication of Graves' disease. I have been in Wales for a week—Welsh Commission business. Hospital filling up after a quiet period.

Sincerely yours,

WM OSLER

One of the saddest losses I have ever had was Revere Osler's death. He had been an undergraduate at Christ Church, his father's college, before the war but it was not until he came back to Oxford on leave that I learned to know and love him. He had all of his parents' charm. F. H. Mosse, the Medical House Officer at the Radcliffe Infirmary, was an ardent disciple of Isaak Walton so Revere frequently visited our mess to discuss fishing for, next to collecting books, this sport was his greatest recreation. Early in September, 1917, Wilder Penfield whom I encountered in Paris while on leave, showed me the letter from Lady Osler [4].

After the armistice I was ordered to take over the laboratory at Base Hospital 33 at Plymouth, England. When I reached London I found that Base Hospital 33 was at Portsmouth and not at Plymouth and that someone had made a mistake in my orders. I saw no reason

1 Royal Society of Medicine

2 Light of your Life (Atala)

3 Pyrexia of Unknown Origin (undiagnosed fever, also called G O K (God Only Knows) until forbidden by Army Orders)

4 A copy of the tragic letter appears in Dr. Penfield's article in this issue. En

why I should not take advantage of the error—the war was over anyway—so I decided to go A W O L at Oxford until the Army caught up with me. I went straight to the Oslers. Their home lived up to its reputation as the “Open Arms” and I was asked to stay until I was found by the military police. Sir William and Lady Osler were then making a brave fight against their as well as our terrible loss of Revere but their interest in former students was unabated. Seeing them again was like coming home and I felt what a great contrast my present devotion was to the awe and timidity with which I had rung that bell in 1913. After a week of bliss Osler came in laughing and said that the Army Headquarters in London had ‘phoned a correction to my orders and that I must go to Portsmouth at once.

The blow of Osler’s death came on December 29, 1919. I learned the bitter news in a newspaper while on the night train to Boston en route to the meeting of the Association of American Bacteriologists at which I was to give my first presentation of a paper—a study of the dysentery organisms I had collected in France, Baltimore, and Birmingham.

Although the Chief had bravely borne the loss of his only son, Revere, who was killed in action in 1917, he had never regained his love of life. Pneumonia and empyema had caused the passing of a man most influential for all that was good, he was noted for his kindly spirit, well beloved as a teacher and physician. The life of Sir William, more than his works, placed him at the pinnacle of his profession. His winning personality, his cheerful disposition, his faith in mankind, but above all his love for his profession made him what he was—the true physician. Perhaps no one was as universally loved or had such an influence for good on the members of the medical profession. Everyone who knew him felt, and felt correctly, that he took a great personal interest in each friend and his problems. Added to these virtues was the fact that from boyhood to his last illness he was a tireless student, an enthusiastic, unceasing worker. His contributions to medical literature included 14 different books and monographs, some 350 journal articles and over 1,000 shorter items, the elegance of style, conciseness of statement and literary quality of his manuscripts marked him as a careful, conscientious writer. His presentations, whether as textbook, periodical literature or spoken word, were examples of masterly English diction. Osler always considered that his greatest contribution to medical education was the introduction of students into the wards and the curtailment of the old lecture system. He often said that he wanted the following epitaph, “He brought the medical students to the wards.” During his long career he was the recipient of practically every honor which the medical profession could bestow.

on those of merit in its ranks, culminating in July, 1919, in the international celebration of his seventieth birthday. The occasion was marked by the felicitations and congratulations of the medical world. A memorial volume was prepared which contained essays by students and colleagues and presented to him by a distinguished committee. In response to the presentation address Osler said,

"To have had the benediction of friendship follow me like a shadow, to have always had the sense of comradeship in work without the petty pinpricks of jealousies and controversies, to be able to rehearse in the sessions of sweet, silent thought the experiences of long years without a single bitter memory fill the heart with gratitude. That three transplantations have been borne successfully I owe to the brotherly care with which you have tended me. Loving our profession and believing ardently in its future I have been content to live in it and for it. A moving ambition to become a good teacher and a sound clinician was fostered by opportunities of an exceptional character and any success I may have attained must be attributed in large part to the unceasing kindness of colleagues and to a long series of devoted pupils whose success in life is my special pride."†

After Sir William's death, Lady Osler made all of his friends and admirers feel that the Open Arms was still their medical home. Atala and I had a delightful weekend there in 1922. Lady Osler was as charming as ever. I also visited her in 1925. It was the last time, as she died August 31, 1928.

Among the letters I received after my appointment at Duke I treasure most the following one from Lady Osler.

13 Norham Gardens

Oxford, June 31d, 1927

Dear Jonah

I am greatly interested in this new scheme of life & future that you have taken on and send my most affectionate & sincere congratulations—for it means of course reward for your hard work here and at the Hopkins—Dr MacCallum was here and told me much of the plans for the new university. I hope you will not find the place too isolated—I would like to ask so many questions—but cannot on paper. Dr Welch is in London and will come here next week and he will be able to tell you everything. You and Atala must be thrilled with thoughts of what a great work is before you. I hope you will be coming over here before you settle down.

†The statement quoted is characteristic of the man. It shows why he was loved, why he succeeded—why his name will appear in the history of medicine as an example of the ideal physician. (J A M A editorial)

Eights Weeks is just over—the weather has been perfect—almost too cool for thin dresses—but the cheeks and lips gave coloring Ch Ch * kept head of the river Oxford has been more beautiful than ever—masses of bloom everywhere Tennis is in full swing everywhere

My love to you both—

Affly,
Grace R Osler

Soon after we moved into our new home in Durham I received an attractive brass door knocker with the following letter Needless to say we greatly prize the knocker which is now on our front door

My dear Dr Davison,

I am sending this quaint little knocker that my sister, Lady Osler, picked up for you in Durham a year ago last summer We were visiting the cathedral there soon after she had heard of your appointment to Duke University You may know the myth of the cathedral being built on a spot where St Cuthbert was buried—his burial place being ordained by some miraculous message as to a “dun-cow” and that there is a huge knocker at the door like this I fear I am rather vague as to the tale but at any rate Lady Osler said “I must get one of those for Davison when he goes to his new home in Durham ” In the unpacking of her trunk this was mislaid and when I was distributing her things in her room I found it She really got it as a joke but I am tempted to send it on to you to show you of her thought and hoping you might like it as a memento

It is very sad to feel that those wonderful days of the “Open Arms” are over but the influence therefrom is spread over the world! Hoping all goes well with you & yours in your tremendous work,

Believe me,
Yours very sincerely,
Susan R Chapin

March 23rd 1929

Sir William's influence did spread all over the world For example, when the Duke Medical School was organized in 1930, the first question to be answered was “Should the professors be men of established reputation who had “arrived” or should the university gamble on promising younger men with a future ?” Fortunately I had heard Osler discuss this question several times and though most people thought of the original “Four Doctors” of the Hopkins as great men, and they were when we knew them after they had made their reputations and that of the Hopkins, they were comparative youngsters when

*Christ Church, one of the Oxford colleges

originally appointed by President Daniel Coit Gilman—Osler was 39, Halsted 37, Welch 34 and Kelly 31—an average age of 35 years Duke might not be able to find the equals of those Hopkins pioneers of modern medicine—fortunately no one will know until after we are dead—but our best chance was under forty years of age. At any rate that explains why the average age of the original Duke medical faculty was 35 years.

One of Osler's most helpful aphorisms was "To study the phenomena of disease without books is to sail an uncharted sea while to study books without patients is not to go to sea at all." It made me realize how essential a medical library was to every medical school, and that although buildings could be built and a staff assembled, a library had to be hunted in the four corners of the earth. As a result, the collecting was started three years before the school opened, and the Duke medical library is now among the best ten in the country.

Osler's writings also allayed the criticism which arose for building Duke Hospital in a town as small as Durham. Fortunately in 1913 he had stated that a large population was not essential and that Marburg in Germany with 23,000 people—half the size of Durham—maintained a medical school of the first rank.

Another suggestion which came from Sir William's interest in medical history was the naming of the Duke Hospital wards for eminent Southern physicians and surgeons. Needless to say a ward was named Osler, on the assumption that his having lived in Baltimore for fifteen years had made him a Southerner.

His personal advice also was helpful. I always have had difficulty in sleeping, so while a medical student I went to Osler for advice. He was very honest and said "I never have been able to go to sleep easily but I have been compensated for it by being able to read many books which I would not otherwise have touched." Naturally I followed his plan and it is amazing how much literature, good and bad, can be covered while waiting for one's eyes to close.

Like all physicians I know that excess weight is dangerous to health and that moderate outdoor exercise probably is beneficial but my efforts to do anything about the matter were half-hearted. After all if Osler could dispense with exercise and live heartily to seventy and if Welch could live in perfect health to the age of eighty-four with only the daily exertion of walking two blocks from his room on St. Paul Street to the University Club for "brunch," an enormous combination breakfast and lunch at eleven o'clock—as well as eating huge dinners—why should others torture themselves with golf, hunting and fishing unless they liked exercise or thought they did, and why should they be miserable with hunger on an insufficient diet—even if it did contain

vitamins—unless they were so fortunate or unfortunate as not to enjoy good food? That was Osler's and Welch's philosophy and I worshipped them

Sir William's views on religion were very comforting to most physicians. He advised his students "All of you will have to face the ordeal of every student of this generation who sooner or later tries to mix the waters of science with the oil of faith. You can have a great deal of both if you only keep them separate. The worry comes from the attempt at mixture." In his Ingersoll lecture on Immortality he acknowledged that he was of "the opinion of Cicero who had rather be mistaken with Plato than be in the right with those who deny altogether the life after death." Osler illustrated the comfort of this belief in one of the last letters written on his deathbed. "The harbour is not far off. And such a happy voyage, and such dear companions all the way! And the future does not worry. It would be nice to find Isaac (his son Revere) there but who knows?"

Hendrick William Van Loon once said that "Luck is about ninety per cent of everything you get in this world." My luck consisted in meeting Osler in 1913. I realize that no reminiscences of mine will, at second hand, convey the enthusiasm for medicine and medical progress which Sir William instilled into every medical student and physician who had the privilege of meeting him, no matter how briefly. All of us need his spirit and faith. We should read and reread Harvey Cushing's *Life of Osler* "in the hope that something of Osler's spirit may be conveyed to those of a generation that has not known him, and particularly to those in America, lest it be forgotten who it was that made it possible for them to work at the bedside in the wards," as Cushing stated in the dedication of the biography.

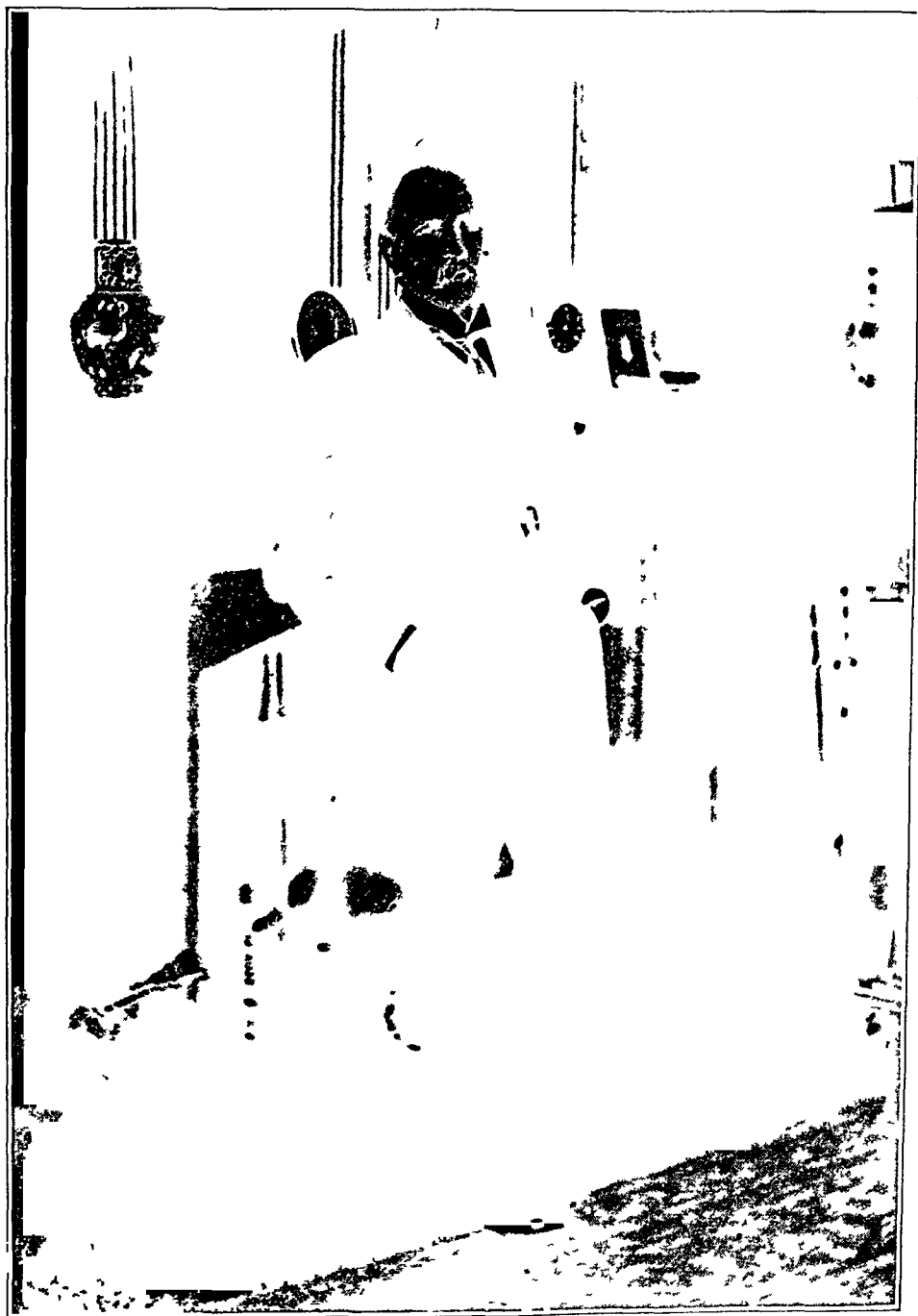


American Pilgrimage to Louis' tomb, Montparnasse, Paris, October 1905

	Whitman	Norton	Pearson	
Kayserling	McCarty	Osler	Magnin	
Klebs	Beyer		Jacobs	Evans
			Knopf	Brennan
				Pottinger
				Lowman



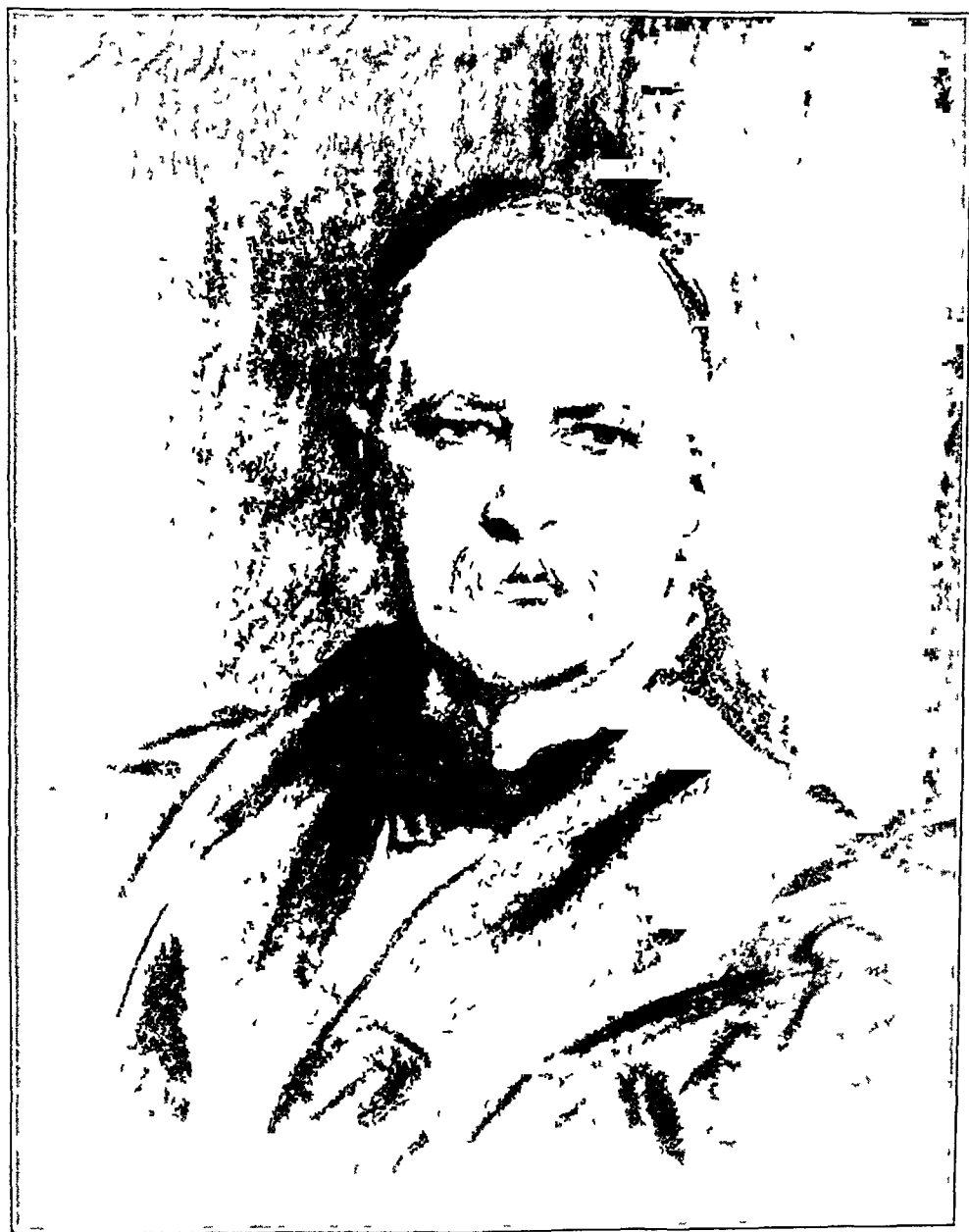
A, Osler with the twin daughters of Dr Whitlocke, his neighbor at Oxford, 1906 B, Osler with two nieces, known in Oxford as "Mrs Osler's decoy ducks," and an Oxford undergraduate, 1909



In the library at 13 Norham Gardens, Oxford. The portraits over the mantel, very indistinct, are those of Linacre, Harvey and Sydenham.



A Dr T R Boggs, Osler, T B Fitcher and Arthur Shipley at City Hospital, Bay View, Baltimore, April 1913 B, Sir William and Lady Osler at the foot of their garden steps at Oxford, 1916



Charcoal drawing made by Sargent for the College of Physicians, Philadelphia, in 1914



A, Col Sir William Osler and his son, Lieut Edward Revere Osler, 1916 B, Osler at the Canadian hospital at Chiveden



A Osler with a Red Cross commandant and two neighbors, 1918 B, Osler in a leisure moment

OSLER AT OXFORD

SIR ARTHUR S MacNALT, KCB, MD, FRCP
LONDON, ENGLAND

I FIRST saw Sir William Osler when he received the honorary degree of Doctor of Science in the Sheldonian Theatre, Oxford, at the Encaenia of 1904. He was in good company—Clifford Allbutt, Jonathan Hutchinson, Marconi, Sir William Macewen, of Glasgow, and others were with him—but Dr Osler received a special ovation. There were already rumors that in view of Sir John Burdon-Sanderson's impending resignation, Osler might be the next Regius Professor of Medicine.

I first met Osler in June of the following year, in the garden of The Lawn, Banbury Road, the residence of the Professor of Physiology, Dr Francis Gotch. It was afternoon, and I was talking with Mrs Gotch and her two daughters. Up the garden path in the sunshine, unannounced, came Dr Osler, clad in professional frock coat and top hat, for he had just returned from a visit to London. He took off his hat and sat in a low hammock hung between two trees, swinging his legs off the ground. He spoke chiefly of his plans for finding a house in Oxford. When he had departed, Mrs Gotch told me of his inspiring influence, which already had done so much to encourage the teachers in the Oxford Medical School.

While in London, working at University College Hospital, I had made friends with Dr W. W. Francis, Osler's nephew, who was doing postgraduate work at Great Ormond Street. In November 1905, I went to Oxford to do a month's work in the department of pathology there, under Prof James Ritchie. Francis introduced me to "The Open Arms," and from thenceforward I was a fervent disciple of my Regius Professor. How the memory of those Sunday tea parties comes back to one! I see Lady Osler, presiding at the tea table with a rare individual dignity that would have adorned a duchess, but kindly and sympathetic with the shyest of undergraduates. The spacious drawing room would be packed with all sorts and conditions of men, university dons, graduates and undergraduates, visitors from Canada and the United States, physicians and surgeons from London, all drawn as by a magnet to that hospitable hearth. For additional attraction to the youth of Oxford there were usually two or three lovely American or Canadian girls, birds of passage who broke under-

graduate hearts in the kindest possible way ere they winged their way back across the Atlantic Every one talked, every one laughed, every one was happy

Amongst it all, passing from group to group, moved our host, talking to each visitor as a personal friend, showing his wonderful memory for faces and for the details of each man's family "How's your father? He told me to keep an eye on you"

At the time of my first visit, the Bishop of London had caused some excitement and indignation by preaching a sermon against the bacchanalian customs of Oxford Solemnly, the Regius Professor, notebook and pencil in hand, went the round of his guests, inquiring of each how many times he had been drunk in the previous week "I'm collecting statistics for the Bishop," he explained One guileless young man said he was a teetotaler Osler shook his head and made a black mark in his notebook "Dear me, was it as bad as that?" he exclaimed, amid general laughter Already, he knew every man working in the medical school and the particular stage he had reached in his course, just as he had done at Montreal, at Philadelphia and at Baltimore Only those who have trod the arduous paths of medicine can appreciate the encouragement which this personal touch afforded Each student felt that his Regius Professor took a special interest in his work and was his friend

During that memorable month I attended the weekly clinic he held at the Radcliffe Infirmary It was chiefly for general practitioners, who came from Oxfordshire and neighboring counties to hear him A patient with some interesting malady would be placed on a couch, and Osler would sit beside him, at first observing and then delivering an exposition of the physical signs I remember, in particular, one afternoon devoted to abdominal tumors, when Osler pointed out the patterns they made on the abdominal walls, and their value in diagnosis

I recollect a witty speech he made at a dinner of the Oxford Medical Graduates Club that year Referring to his being put rapidly through the stages of matriculation to graduation in receiving the Oxford degree of Doctor of Medicine, he said it reminded him of the untrue things people sometimes said about medical graduation in certain American universities¹

In 1906 he came to a meeting of our medical society at University College Hospital to deliver a lecture on the advantages of a medical society The Oxford men at the hospital entertained him beforehand at a little dinner This was his reply to my invitation

Dear MacNalty Kind boys! Yes of course I will dine with you—Trocadero—anywhere Send me word Sincerely yours, Wm Osler P S Any hints about the Society?

And, in a subsequent letter

Do not order much dinner—at least not for me—I have been on the “bread of affliction” for a week with a gastro-duodeno-jejeuno-ileo-colic catarrh of Irish extraction

Nevertheless, Dublin hospitality had not affected his high spirits, for he was full of fun and jest at our little dinner, and gave a delightful lecture afterward

At the final examination for the degree of Bachelor of Medicine at Oxford in 1907, Dr Osler's innate kindness cheered us through the ordeals of written papers, practicals and orals. All the candidates felt that he was as anxious for each one of us to do well as if he had been a personal relative. The smile, the jest and the inquiry as to how we had got on helped us greatly. Bending over a patient with heart disease, on whose case a full clinical report was asked for, the candidate unexpectedly would find the Regius Professor at his elbow and a hand laid on the patient's precordium. “A good thrill, that—that's a nice case to have,” would be the comment, and Osler would pass on to cheer another victim. British examinations are too often rigid and formal, Sir William lightened them for the candidates by the “human touch”

He came out of the Radcliffe Infirmary one morning and greeted the waiting candidates. “I've just been over the cases with the examiners,” he said. “Now I'll tell you what you're going to get!” The ever gullible knot of men surged round him. “They're chiefly actinomycosis and madura foot,” he said, with a twinkle in his eye, and departed, chuckling

His son, Revere, was then at Winchester College, and on his next visit to Winchester Osler remembered to call on my father, who was in practice there, to say a kind word about me. He would have done the same for the father of any other Oxford man, the incident is mentioned only as one more instance of his generous disposition

His reception of my thesis for the degree of Doctor of Medicine, in 1910, must be one of the most unconventional on record. I wrote to the Regius Professor for an appointment, in order to submit the manuscript to him. In reply, he said that he would not give me the trouble of coming especially to Oxford, as he would be in London the following week, and he invited me to tea with him at the new Royal Automobile Club. When we met at the Club, the Regius was accompanied by a Canadian physician and his wife, to whom he was showing the sights of the metropolis. The club's guest room was not yet opened, so we went on to a fashionable teashop in St James's Street. And there, amidst the tinkle of teacups, the buzz of light conversation

and the strains of "The Merry Widow" waltz, Sir William turned over the pages of my thesis and discussed the Pel-Ebstein syndrome with me. A few months later, he presented me for the degree. There were two candidates, Sir Henry Tidy and myself, we lunched with Osler beforehand, and he took us in his car to the Sheldonian Theatre for the ceremony. Thus he gave up his time to his students, to make it one of the most pleasant of memorable days in their lives.

Sir William was pleased when John Burns appointed me a medical inspector of the Local Government Board. He always entertained a high opinion of the board's medical reports and monographs, considered that they formed the basis of modern medicine and lamented that they were so little read. Under the direction of Sir John Simon and his successors, Burdon-Sanderson, Thudichum, Klein, Horsley, Horder, Gordon and Houston, all the workers did outstanding pioneer work in pathology, with the aid of small scientific grants from the board.

My new work brought me in touch with Osler from time to time. His interest in measures for the combating of tuberculosis in America is well known, and this interest was equally vigorous and active when he crossed the Atlantic. Soon after he came to Oxford, he began to plan for an Oxfordshire branch of the National Association for the Prevention of Tuberculosis. In 1909 he organized a tuberculosis exhibition in the University Examination Schools, with lectures, medical conferences and two big general meetings. Miss Mabel Price, the daughter of a former master of Pembroke College, was an energetic secretary of the new branch, and in 1910 the first dispensary was opened at the Radcliffe Infirmary, with Dr William Stobie, trained under Sir Robert Philip of Edinburgh, in charge, and two nurses. Within the next two years seven other dispensaries were opened in the county. But Oxford and the county had no sanatorium or tuberculosis hospital, although Osler collected some funds toward it and a property was bought at Shotover. Sir William came regularly to the Oxford dispensary and saw patients there, in consultation with Dr Stobie. He expended much time and a considerable part of his income in helping the work of the Association. This voluntary work was of great value, but after 1912 the position changed. A National Tuberculosis Scheme, supervised and subsidized by the Local Government Board and administered by the local authorities, was in force, and subscriptions to voluntary organizations diminished. Then came the war, and Sir William naturally felt that he could not continue being the main financial support of a service which was a public health responsibility. I mentioned this difficulty to my chief Sir Arthur Newsholme, and then, at Osler's invitation, went to spend a night

with him at Norham Gardens to explore the situation. That was in 1915, and the shadow of war hung over that familiar household. The staff of servants was diminished, Revere was serving in France, Sir William had no secretary and sat down at his desk after dinner to cope with his heavy correspondence, writing each letter and postcard himself. Both he and Lady Osler had a presentiment that their son would never survive the war, and, though they strove to put on a brave face to the world, this haunting fear was ever in their minds.

That night Sir William, Dr Stobie and I discussed the question of tuberculosis in Oxfordshire. I may add that I was successful in relieving the Regius of his financial burden, and that the Oxford Corporation and the Oxfordshire County Council took over the responsibility for the work. It was appropriate that in after years the Oxford Sanatorium at Headington received the name of "The Osler Pavilion." I recall one more incident of this visit. Sir William had followed King George V's example in becoming a total abstainer at the outset of the war. As we drank our glasses of soda water before going to bed, he made a wry face. "It's a cold, dull drink, Mac," he said.

During this and on subsequent visits to Oxford, Sir William showed me the treasures—incunabula and first editions—of his library, and explained his system of cataloguing. One of my cherished possessions is a copy of the "*Bibliotheca Osleriana*,"¹ edited by Dr W. W. Francis, R. H. Hill and Dr Archibald Malloch, which Lady Osler bequeathed to me. She also gave me two books from those in Sir William's library which were not to go to McGill University.

In the busy and strenuous years of the war I saw Sir William only occasionally. Sorrow had whitened his hair and lined his brow, but he carried on with his work, wearing a brave face to the world. In 1918 a new quest brought teacher and pupil together once more.

In the course of the months of March and April of that year, a number of cases of an obscure disease, characterized usually by stupor or lethargy and by ophthalmoplegia, were reported in England. A detailed investigation of the outbreak was made under the auspices of the Local Government Board and the Medical Research Committee, Prof. J. McIntosh and Professor Marinesco studying the pathology and Col. S. P. James, M.D., the epidemiology, while I was responsible for the field investigations and the clinical aspects of the inquiry. I early sought Sir William's counsel and advice on the subject. He took an active and personal interest in the progress of the investigation, and was at first inclined to regard the cases as examples of Heine-

¹ Osler, W. *Bibliotheca Osleriana. A Catalogue of Books Illustrating the History of Medicine and Science*, Oxford, Clarendon Press, 1929.

Medin disease or of a cerebral type of acute poliomyelitis Here is one of his letters to me, dated June 11, 1918

Dear MacN Where in London are most of the polio cases? We have one in the Radcliffe, very remarkable & possibly another I was in Leicester last week where they have 5 or 6 I shall be up Friday & Monday Yours, Wm Osler

I arranged to take Sir William to the London Hospital, where the wards contained a number of patients with the new disease On June 14, he appeared early in my room at the Local Government Board, carrying what he termed "a fine big bundle" of literature on Heine-Medin disease, which he lent me He then went through the notes I had collected and made on my own cases and the manuscript of my report of the malady, constantly helping me with criticisms and observations drawn from his vast store of experience and knowledge After a hasty lunch at a "bun shop," we proceeded to the London Hospital, where we saw 12 representative patients, each of whom Sir William examined thoroughly Next, we went to the laboratory, where we discussed the disease from the pathologic standpoint with Professor Bulloch and Dr McIntosh We traveled to Oxford together, and Osler insisted on my being his guest at Norham Gardens We talked about encephalitis all evening, until Lady Osler intervened and insisted on our going to bed On the following morning, Sir William demonstrated a most interesting example of the malady, with choreiform movements, and in the afternoon he gave, in the Anatomical Theatre, a lecture on the general subject of Heine-Medin disease (epidemic poliomyelitis) before an assemblage of medical officers and practitioners It was a great contribution to our knowledge, I regret that he never published the lecture In delivering it, he gave an instance of his great and open scientific mind In our discussions about the obscure disease, I had ventured, with some temerity, to point out that all my investigations had so far tended to show that we were dealing in the epidemic outbreak with a disease which differed from the cerebral form of poliomyelitis Indeed, my co-workers and I had arrived independently at the conclusion that it constituted a clinical entity Subsequently, Kinnier Wilson and Buzzard adduced evidence supporting our conclusions, and later we were in a position to add that the disease as it appeared in this outbreak was identical with encephalitis lethargica, described by von Economo, of Vienna, and Netter, of Paris Our findings were recorded in a special report to the Local Government Board, published in 1918 But in June we were only proceeding toward this conclusion, and Sir William's lecture had been based on the opposite point of view Yet he alluded in the lecture to the fact that fresh evidence was leading him to reconsider the matter, and in the article

on encephalitis lethargica which he wrote for his textbook shortly before his death, he gave me full recognition for work on the subject

Through Sir William's good offices with the Surgeon General and the Chief Surgeon, American Expeditionary Forces, we obtained the advice of Dr George Draper, the authority on poliomyelitis, then serving as major with the Medical Corps of the United States Army in France. Dr Draper came over and visited, with me, many areas in different parts of the country where the disease was prevalent, and gave us the benefit of his experience with the cerebral form of poliomyelitis and of his opinion of the epidemic cases.

This account will have been of little purpose if it has not shown how Osler selflessly helped others to search out the problems of disease. It is something to be able to say that one has worked with Osler, and I shall never forget how he encouraged and aided me in a most difficult and responsible task. He cherished the student spirit to the end. It was at his suggestion that Dr Archibald Malloch and I collaborated in an article on influenza in "Nelson Loose-Leaf Medicine,"² Dr Malloch writing the pathologic and clinical accounts, while I was responsible for the history and epidemiology.

On March 24, 1919, I heard Sir William give an address on acute pneumonic tuberculosis at the Tuberculosis Society in London. He was as cheery and jocular as ever in greeting me after reading the paper, but he had grown thin and careworn. The sword was wearing out the scabbard. We subscribed to his *Festschrift*,³ and the Oxford Graduates Medical Club entertained him at dinner to commemorate his seventieth birthday. He said, in reply to the enthusiastic toast of his health, "I have worked hard all my life," and with pardonable pride he added "There must be good rubber in my arteries, or I should not now be among you, still working at three score years and ten."

We had hoped to have him longer with us to lead and inspire, but it was not to be. That year, in Jersey on his holiday, he went bathing and swimming in the sea. In October the news came that he was stricken with illness, after traveling from Scotland by car during the railway strike. I had been appointed Examiner in Public Health at Oxford, and Sir William had invited me to stay at "The Open Arms" during the examination. I wrote to Lady Osler, saying that of course I must go elsewhere, but she replied that Sir William insisted on my coming. I saw him twice in the course of my short visit. He hailed me with his usual cheery greeting, but the hand of illness, which he

² MacNalty, A. S., and Malloch, A. Influenza in Nelson Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1928, vol. 1, chap. 15, pp. 583-638.

³ Contributions to Medical and Biological Research, dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919.

had done so much to ward off for others, had seized him, and he had occasional fits of coughing. Of late years he had been especially susceptible to attacks of influenza. He had written to me earlier in the year

I have had a pleo-polymorphic-cocco-bacterio-bacillary-upper-respiratory-passage infection lately. I have had all I can do to keep it from reaching my gray cortex through the cribriform plate.

While I was at his bedside, which was strewn with books and pamphlets, for he read and wrote whenever he could elude the vigilance of Lady Osler and his nurses, Dr. A. G. Gibson came in to tell him that Pfeiffer's bacillus had been isolated from his sputum. He seemed pleased, "I knew," he said, "there was a nigger in the wood-pile." Then he asked about the examinations. "Be lenient to them, make allowances for the ordeal you are putting them through," he urged, ever thoughtful for his students, a counsel which I have endeavored to bear in mind when examining. At my second visit, one of farewell, I found him a little weaker. He talked to me of Victor Horsley, with whom I had formerly worked at University College. He read me his charming and sympathetic review⁴ of Stephen Paget's "Life of Horsley," which he had written in pencil for the *Oxford Magazine*. The last thing he wrote for publication, it ended appropriately with the well known quotation from Shelley's "Adonais," beginning, "He has outsoared the shadow of our night." I did not stay long, for I feared to tire him. At our parting handclasp I think we realized that we were parting in life for the last time.

The end came that same month, in the afternoon of December 29. I represented the Ministry of Health at the impressive service in Christ Church Cathedral on Jan. 1, 1920, when men and women from all parts of the Kingdom gathered to pay their last tribute to the beloved physician.

In noting these memories of Sir William, my aim has been to show how his noble personality, his generous heart and his stimulus helped and inspired his fellow men, for what he did for me he did for countless others who came under his sway. Alike at the Universities of McGill, Pennsylvania, Johns Hopkins and Oxford, he exerted his influence for the good of students and for the advancement of medicine. In this centenary year of his birth, many, like myself, must be thinking anew of William Osler and of all they owe to him. As I have written elsewhere, "He achieved many honors and many dignities, but the proudest of all was his unwritten title, 'The Young Man's Friend'."

⁴ Osler, W. Sir Victor Horsley (book review), *Oxford Magazine* 38 175 1920

A DAY WITH DR OSLER IN OXFORD

WALTER L. BIERRING, M.D.
DES MOINES, IOWA

FROM some travel notes, a few leaves are taken to recall a happy day spent with Sir William Osler at his home in Oxford. It was one of the later days in July, a time when all England is beautiful, the green hillsides, fields of hops and grain, picturesque ivy-covered houses and enclosed English gardens formed such an interesting landscape that the two hours' ride from London to Oxford passed rapidly.

My traveling companion, Col. Louis A. LaGarde, Medical Corps, United States Army, and I arrived at the luncheon hour. Lady Osler was at the station with her Franklin car. There were two other visitors, Col. and Mrs. Richard P. Strong, in civil life, Colonel Strong was Professor of Tropical Medicine at the Harvard Medical School.

We were soon at 13 Norham Gardens. Dr. Osler met us on the veranda with a greeting such as only he could give. He may have been Sir William to others, but to us he was still the same Dr. Osler we knew in the good days before he came to Oxford in 1905.

We were aware that the medical world, a few weeks before, had taken notice of his seventieth birthday. At a brief and touching ceremony in London on July 11, with Sir Clifford Allbutt presiding, two memorial volumes had been presented to Dr. Osler.¹

Sir Clifford, who was Dr. Osler's brother Regius Professor (at Cambridge) had spoken of the memorable occasion as "one anniversary of many years of supreme service in two kindred nations and for the world." With his more than 80 years, Sir Clifford had made jocular reference to his "youthful" colleague.

Colonel LaGarde and I, too, could have testified that age had dealt kindly with Osler, although he told us of having spent a week in bed after the birthday ceremony, in "another bout with the pneumococcus." The black mustache had changed to gray, but otherwise the last fifteen years seemed to have passed unnoticed. In the old-time twinkle of the eye, the winning smile and the elastic, boyish activity, we saw the Dr. Osler his American friends had always known.

Colonel LaGarde and Sir William were old friends. They had been born in the same year, so in their greeting there was much banter as to youthful appearance and the like. Sir William recalled the

¹ Contributions to Medical and Biological Research, dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919.



Dr Walter L. Biering, Osler and Col Louis A. LaGarde, at 13 Norham Gardens, July 30, 1919. This is the last known photograph of Dr. Osler.

interesting work of LaGarde on ballistics and poisoned wounds,² done in the laboratory of Dr William H. Welch in Baltimore twenty years before

In Osler's many inquiries about American colleagues, one appreciated how he still entertained the warmest sympathies for America and her institutions, associated as they were with some of his happiest memories. One of his first questions was, "How is my old friend (James T.) Priestley? Tell him I just picked up several fine old works of his ancestor, Joseph Priestley." He was interested to learn that the two grandsons of his friend (Joseph B. Priestley, M.D., now of Des Moines, Iowa, and James T. Priestley II, M.D., now of the Mayo Clinic, Rochester, Minn.), had entered the University of Pennsylvania, where once their distinguished ancestor was associated with the medical faculty.

We marveled at Dr. Osler's memory and knowledge of details of the various happenings in medical circles in America. He seemed to know so much about old friends and the service that each had rendered during the war period. Many had called on him, Oxford had evidently been the mecca for Americans during the previous five years. Lady Osler informed us that her maid had kept a record of the visiting Americans to whom tea had been served. The number was over 1,600.

Two special hospitals for the treatment of cardiovascular diseases and orthopedic conditions had been established in Oxford during the war, and a large number of American medical officers were stationed there from time to time. Lady Osler referred to the great pleasure it gave Sir William to have these fine young men about him. Many of us remember his particular affection for the younger members of the profession, and the medical officers who were so fortunate in being associated in service with Dr. Osler have treasured the memory of the experience.

Sir William was looking forward that day with interest and pleasure to meeting his many American friends the following year in New Orleans at the Annual Session of the American Medical Association.

After luncheon, we wandered about the beautiful garden and interesting home with its treasure store of books, later, under the guidance of Lady Osler, we saw a bit of the University that Oxford means to most of us. There is a particular charm about Christ Church, Merton, Magdalen, Pembroke, Balliol, Queen's, University, Oriel and the other colleges that form the University of Oxford, some are mellow with age, while others belong to the newer group, but about all there

² LaGarde, L. A. *Poisoned Wounds by the Implements of Warfare*, J. A. M. A. 40:984 (April 11), 1062 (April 18) 1903.

cluster many interesting traditions of leading personages in English history. Lady Osler particularly desired us to visit the Latin Chapel in Christ Church Cathedral, where an interesting military wedding had taken place a year before, on June 29, 1918. Major Reginald Fitz of Boston had married Miss Phoebe Wright of Ottawa, Ontario, Canada, each was the child of old friends, and on leave from France at the time. Lady Osler told of the bride's being given away by Sir William, and of the reception and tea that followed on the terrace at "The Open Arms," the Osler's home at 13 Norham Gardens.

"That they should have arranged for this wedding," says Cushing,³ "was not only characteristic of the Oslers but expressive of the warmth of feeling which England as a whole felt towards America."

There was a short visit to the Bodleian Library with hardly more than a glimpse at its literary treasures. Dr. Osler had been named one of the curators soon after coming to Oxford in 1905. The duties must have been an attractive part of his new environment.

Although he had to assume many new obligations during the war period, his interests and sympathies continued to be directed to promoting the highest ideals in medicine. His deep interest in the purpose of our visit was one example.

For a long time the idea had been in the minds of the leading clinicians and medical educators in the United States that the best means to elevate the standards of medical practice was to develop on a national scale a central qualifying board, expressive of the highest type of medical training in our country. As an outgrowth of this sentiment, the National Board of Medical Examiners of the United States was established, in 1915.

Dr. Osler had often expressed his interest in qualifying examinations and in the need for a more practical character of such test. His address on "Examinations, Examiners, and Examinees," at the opening session at St. George's Hospital,⁴ had been a vigorous appeal for reform, in this and in later writings, he severely criticized the high percentage of failures (often 60 per cent) in the examination for fellowships in the Royal College of Surgeons of England. In the address appeared several expressions on examinations in general that may be applicable to this later day. "As the best means to an end, they may be the best part of an education, or its worst—they may be the very essence of its ruin." "Helpful, if an integral part of the training, they may, and do, prove the intellectual ruin of many good men."

³ Cushing, H. *Life of Sir William Osler*, Oxford, Clarendon Press, 1926.

⁴ Osler, W. Address on Examinations, Examiners, and Examinees, *Lancet* 2 946 (Oct. 1) 1913.

With the close of the world war, the time seemed opportune to have a committee of the National Board in the United States make a comparative study of qualifying examinations as conducted by the Royal College of Surgeons, the Conjoint Board of England and the Triple Qualification Board of Scotland. The further object of the mission was to acquaint the members of these bodies with the aims and purposes of the National Board, with a view to bringing about some form of reciprocal understanding between their country and ours in matters of medical education on the basis of the examination conducted by the National Board. The committee consisted of Col Louis A. LaGarde, Col Victor C. Vaughan and myself. Col Vaughan was detained at home by reason of the death of his son, which had occurred in Tours, France, just before our sailing.

In previous correspondence, Sir William had been most helpful with advice as to the manner of approach and general procedure, and on this day he expressed gratification over the favorable impression that our mission had evidently accomplished. The committee had decided to include in its report a recommendation that the National Board extend an official invitation for a British commission of three members, representing the qualifying bodies of England and Scotland, to come to the United States during the following year for a study of our leading medical schools and teaching hospitals and to attend a National Board examination in Philadelphia. The advice of Dr Osler was again helpful in selecting the personnel of this proposed commission, and with his approval the names of the following men were submitted: Sir Humphrey Rolleston, of the Royal College of Physicians, Sir Holburt J. Waring, of the Royal College of Surgeons and representing the Conjoint Board of England, and Sir Norman Walker of the Royal College of Physicians, Edinburgh, as the representative of the Triple Qualification Board of Scotland. Sir William was most encouraging in his prophesies as to the outcome of these mutual visits. He recognized their far reaching importance, not only in forecasting still further exchange of professional relations between the two English-speaking nations, but in advancing the higher ideals of world peace and human welfare.⁵

5 The members of the British commission, on their return in 1920, rendered a report to the Conjoint Board of England and the Triple Qualification Board of Scotland that the educational methods in the United States and the National Board examinations were satisfying, and recommended that the diplomates of the National Board be admitted to the finals of the two British qualification boards, similar action was taken by the National Board with reference to certification from the two British qualification boards mentioned, thus establishing for the first time a reciprocal agreement in matters of medical education between the two countries.

Our committee had had the opportunity to study the several plans for postgraduate medical study in England and France, and particularly in London

In the previous year the Fellowship in Medicine had been organized under the chairmanship of Dr Osler. With the cooperation of the medical schools and hospitals of London, general and special post-graduate courses of study were arranged, as well as the provision of research and clinical assistantships. These were of immediate benefit for medical officers overseas from Canada and the United States. A weekly bulletin was being issued, listing the courses, clinics and other information.

In April 1919 the Post-Graduate Medical Association had been organized, with Sir William as president, further to coordinate post-graduate medical study in London. At our visit Sir William spoke at length on the need of combining the two organizations concerned with postgraduate education.⁶

He was enthusiastic about the rapid progress being made in the project of the American Hospital for Great Britain, of which Lord Reading was chairman, the financial requirements seemed to be assured and ample to build a large hospital of the most modern type, with research laboratories and complete facilities for clinical teaching.

The large number of activities in which Dr Osler maintained an interest was a marvel to all who knew him.

Sir William and Lady Osler were making ready to leave the next day for a holiday on the island of Jersey. It had been a summer of peace and victory celebrations in England, but they were looking forward to this first opportunity for real relief from the great strain of the past five years. The war had brought the keenest sorrow to the Osler home, in the loss of an only son. This sadness did not find expression in words, although it was in the thoughts of all that July day. It was this quiet heroism in the aftermath of the great war, reflected in so many English homes, that more than all else engendered a stimulating hope for the future of that sturdy race.

The hour had come to say adieu. There was that in the words at parting—"Mighty glad that you boys came out"—and in the final wave of the hand which left a delightful impression of our visit to Oxford, to be more treasured with the passage of the years.

2840 Ridge Road

⁶ The amalgamation was accomplished on Oct 24, 1919, and the weekly bulletin was issued under the combined sponsorship of the Fellowship of Medicine and the Post-Graduate Medical Association. After the death of Dr Osler, on December 29, Sir Humphrey Rolleston succeeded to the presidency.

WILLIAM OSLER, THE HUMANIST

JOHN F. FULTON, M.D.

NEW HAVEN, CONN.

IN HIS lifetime William Osler probably exerted a wider influence on his contemporaries in medicine than any other man of his generation, and now, when physicians of America, Canada and Britain are celebrating the centenary of his birth, one must ask oneself why it was that Osler came to have such an enormous following. His discoveries were few—in the sphere of new knowledge, the blood platelets and several obscure clinical syndromes are all that can really be credited to him—and he had the doubtful distinction of having written a highly successful textbook, which has now passed through eighty-four printings. Actually, his major contributions were twofold. The dedication of Harvey Cushing's "Life"¹ succinctly points out the first of these.

TO MEDICAL STUDENTS

in the hope that something of Osler's spirit may be conveyed to those of a generation that has not known him, and particularly to those in America, lest it be forgotten who it was that made it possible for them to work at the bedside in the wards.

However, Osler lives today not only because he brought medical students into the wards but for a much more important reason, namely, that he was one of the greatest medical humanists of his time. He surrounded himself with the writings of all the great characters in the annals of medicine and science, beginning with the classics, and the inspiration he drew from them is perfectly expressed by another great humanist in science, the late Sir D'Arcy Wentworth Thompson².

When a man reads the classics for pastime and refreshment, the last or farthest end of knowledge (as Bacon called it) is not the question, it is enough if he seek to entertain his mind with variety and delight. We pick up a familiar volume, it opens at an accustomed page. Presently we sail beyond the sunset

The Sixth Frank Billings Lecture, delivered at the joint meeting of the Institute of Medicine of Chicago and the Society of Medical History of Chicago, Feb. 25, 1949.

1 Cushing, H. Life of Sir William Osler, Oxford, Clarendon Press, 1926.

2 Thompson, D. W. Science and the Classics (address to the Classical Association, April 9, 1921), in Science and the Classics, Oxford University Press, 1940.

with Ulysses, or hear the battle rolling by the sea, or in the stateliest measure ever moulded by the lips of man, hear kine lowing and bees humming in Italian pastures, mid wheat and woodland, tilth and vineyard, hive and horse and herd, or Ilium falling, Rome arising, and the walls of Carthage and the blue waters of the Tuscan Sea. The old woman with her Bible on her knee is doing just the same. Her eyes are anointed with a divine clay, two thousand years roll back as it were yesterday, and her place by the fireside becomes holy ground.

Osler himself might well have written this passage, for he was familiar with "the wild strains of passion" of Catullus and with the "melancholy, long, withdrawing roar" which Socrates heard long ago on the Aegean and which Matthew Arnold captured for all time in the inspired lines of "Dover Beach." What the old masters gave to Osler he passed on with vividness, adding something of himself each time. He could portray men such as John Caius, Thomas Linacre, François Rabelais and Thomas Sydenham as though they had lived yesterday, and he also rescued from oblivion many obscure figures in medical history—John Y. Bassett, the Alabama student, Thomas Dover, whom he styled "Physician and Buccaneer," and Elisha Bartlett, the Rhode Island philosopher. As Edward Streeter wrote after Osler's death³

He reinvested all his favoured ones with historic reality, launched them from his humanity as genuine forces in the world of science no longer lying embalmed in the imagination of the studious, but redelivered, given voice again in the land of the living. He shared Browning's power. "The life in him abolished the death in things."

Osler tells the story of how he became interested in books in an introduction entitled "The Collecting of a Library," which he began during his last illness (but did not complete) for the catalogue of his library. His father, a country parson, had a library of some 1,500 volumes, made up principally of theological works but also containing a number of old books, such as Stow's "Chronicle" and a Breeches Bible. Later the Reverend W. A. Johnson, Warden of the Trinity College School which Osler attended in Ontario, stirred his interest in scientific books and in microscopy. Johnson had a rare gift for imparting knowledge and inspiring enthusiasm—a gift, he it said which he passed on to his apt pupil in full measure.

During 1867-1868, Osler spent a year at Trinity College and there crossed the path of Dr. James Bovell, a friend of Johnson's. With Bovell he spent Saturdays, making microscopic sections and collecting botanic specimens. Euripides and Livy now seemed dull by comparison, and in October 1868, at the age of 19, he entered the Toronto School of Medicine. The following year brought him a great oppor-

³ Streeter, E. C. Osler as a Bibliophile, Boston M. & S. J. **182** 335-338, 1920.

tunity, for Dr Bovell, whose family had gone to the West Indies, took the young student into his house. It has been said that "the privilege of browsing in a large and varied library is the best introduction to a general education"⁴. Dr Bovell had just such a library. "The best the human mind has afforded was on his shelves, and in him all that one could desire in a teacher—a clear head and a loving heart"⁴. Bovell had a special passion for the great physician-naturalists, and during the long winter evenings of 1869 young Osler became familiar with many of the masters. He later commented that "the diet was too rich and varied and contributed possibly to the development of my somewhat splintery and illogical mind, but the experience was invaluable and aroused an enduring interest in books."

The first book he purchased for himself was the Globe Shakespeare, and the second, the Ticknor and Field edition (1862) of the "Religio Medici," which was to be his *comes viae vitaeque* (and which rested on his bier in Christ Church after his death but was not, as is often said, cremated with him). His library grew slowly, as he was impecunious, but during his first trip abroad, in 1873, he was able to acquire some of the more important English and German medical texts. Because of his various moves, however, little remained of his Montreal library at the end except the 1862 "Religio." While in Philadelphia, from 1884 to 1889, he became a member of the library committee of the Philadelphia College of Physicians, on which Weir Mitchell also served, and it is probable that Mitchell spurred on his interest in collecting a personal library. The general atmosphere in Philadelphia was literary, for in college circles everyone wrote, and Osler recorded that his pen and brain "got a good deal of practice."

After he settled in Baltimore his library grew rapidly, and he was prompted to observe

a library represents the mind of its collector, his fancies and foibles, his strength and weakness, his prejudices and preferences. Particularly is this the case if to the character of a collector he adds—or tries to add—the qualities of a student who wishes to know the books and the lives of the men who wrote them. The friendships of his life, the phases of his growth, the vagaries of his mind all are represented.

Osler bought original editions of the great writers in science and medicine, early books and pamphlets relating to his profession in America and, finally, the works of general authors, such as Milton, Keats, Shelley and Sir Thomas Browne. Buying as extensively as he did and subscribing to more than forty journals, he soon had the house overrun.

⁴ Osler, W. *Bibliotheca Osleriana. A Catalogue of Books Illustrating the History of Medicine and Science*, Oxford, Clarendon Press, 1929.

Then came his removal to Oxford, where he found leisure and much greater opportunity for filling important gaps in his collection. As the library grew, the plan for its catalogue gradually crystallized in his mind. It was to have a definite educational value and literary and historical interest, and he conceived the highly original scheme of arranging the foremost authors in chronologic sequence, to give the student an easy grasp of the historic developments in medicine.

Faced with a bewildering variety and ever-increasing literature, how is the hard-pressed student to learn—first the evolution of knowledge in any subject, and secondly, the life and work of the men who made the original contribution? The idea is to have in a comparatively small number of works the essential literature grouped about the men of the first rank, arranged in chronological order.

The fundamental contribution may be represented by a great Aldine edition, e.g. Aristotle, by the brief communication such as that of Darwin and Wallace in the *Proceedings of the Linnaean Society*, 1858, or by an eight-page pamphlet of Roentgen.⁴

His decision to divide the catalogue into eight sections, arranging the chief works chronologically, was horrifying at first to some of his librarian friends, but he gradually won them over. He had intended to introduce each of the eight sections with a preface, but these were never written and the editors decided not to attempt them. Division of the catalogue into sections made necessary a comprehensive index, which, even though set up in small type and in triple column, ran to eighty pages. This remarkably accurate index is an indispensable reference tool for anyone delving into the history of medicine.

These plans for the "Catalogue" were made sometime before the First World War, and he had written many of the annotations, but when the war came he had thousands of interruptions, and he died in 1919, before the work of assembling his notes was actually begun. Fortunately for posterity, Dr. W. W. Francis, Osler's scholarly nephew, was able, from 1922 to 1928, to devote himself unremittingly to the task, and the catalogue was eventually published in 1929, at the time of the opening of the Osler Library at McGill.

Dr. Francis, and those who assisted him with the editing (especially Reginald H. Hill), scrupulously transcribed all of Sir William's erudite and often amusing annotations, so that there emerged a *catalogue raisonné*, similar to Ferguson's "Bibliotheca chemica," with biographic and bibliographic notes for nearly all the main entries. The human touches thus imparted make the catalogue not a mere census of books but the living record of the man himself—his interests and loyalties and the turns of his mind. By way of example, I should like to cite one of the annotations, that for a medical bibliography through the letters *A* and *B*, published in 1834 by one James Atkinson of York, for whom Osler had a particular admiration.

If we can imagine a conclave of bibliographers in the Elysian Fields presided over by Rabelais, one of the most welcome members would be a man who had done but little to make a great name, but who had, like the chairman, done more to enliven a dry subject than any other member of the assembly. The name of James Atkinson is probably unknown to a majority of my readers. He was quite unknown to me until I accidentally picked up a volume a few years ago, "Medical Bibliography, A and B." The dedication which I here reproduce ("To all idle Medical Students in Great Britain sit—" with a picture of the *sacrum*) had a smack of the Cure of Meudon about it that promised much and then that a man should publish a two-letter bibliography was in itself a stimulus.

While the Osler "Catalogue" was going through the press, there occurred an amusing incident, which indicates that a bibliographer's way is not strewn with roses. Dr Francis discovered one day, when the "Catalogue" was in page proof, that Noel des Quersonmieres, the author of item no 2446, used "Noel" for his surname, hence, his work could not be listed with the D's. That left Dr Francis with a blank he had to fill in or be faced with the task of renumbering all the entries thereafter. I was therefore dispatched to London, with the admonition that I must not return until I had found a rare book whose author's name began with "Des." As luck would have it, I happened on just the thing, the "*Histoire médicale de l'Armée d'Orient*," by Baron René Nicholas Dufriiche Desgenettes, published in 1802. Having great interest as an item of Napoleonic medicine, it proved to be an important addition to the Osler Library and, I am sure, did much to cement my friendship with Dr Francis.

The influence of Osler's humanistic approach has been far reaching. There are certainly hundreds of persons today, throughout the North American Continent and in Britain as well, who can trace their interest, great or small, in the history of their profession to some impetus given by Osler, and who, urged on by his example and enthusiasm, have committed their ideas and findings to paper. Although I never knew Sir William personally, he remains for me, as for many others, a living voice which speaks from the pages of his essays and his catalogue, and I think he has influenced my life more than any other mentor. I first met him—and I use the word "met" with intent—in 1921, when I arrived at Oxford and Lady Osler generously gave me access to Sir William's library. She was the soul of hospitality, and anyone genuinely interested in Sir William's books received a cordial welcome at 13 Norham Gardens. There, during the next four years, I came to know him almost as intimately as if I had met him in the flesh, for his books were in a very real sense a part of himself. He loved them as he did his kin, and there is scarcely a volume in that rich collection that does not bear some evidence of his interest and affection.

To me it was a new world, and I recall the thrill of browsing among those books as vividly as if it had occurred yesterday. Here were the great landmarks of medicine and science, each one with a biographic note or anecdote inserted, often in Osler's own hand. Here was the whole heritage of our great profession within easy reach. In the background was a gracious and kindly woman, who, although bereft by the recent loss of her only son and her husband, had but one thought in life, namely, to see to it that Sir William's plan for his library should be realized.

Not only were the books annotated, but Sir William also had had the habit of inserting correspondence about them. One afternoon I opened a copy of John Aikin's "An Essay on the Relation of Natural History to Poetry" and found therein a letter from Sir Walter Fletcher. It so aroused my interest that I copied it out on a card and forthwith began to collect everything that I could about the Warrington group in general, and about Joseph Priestley in particular. The text of the letter dated March 1, 1918, was as follows:

Dear Osler, I am sending the Aikin today to you. I am delighted to have any chance of filling a gap for you, even by such a trifle. You will admit that you make it very hard to find any joints in your harness! If you want all Aikin's things, will you put on a postcard what you have already, and I will challenge myself to find some more if I can?

It would be great fun to work at that Warrington circle. Some day I must get out of the train at that now horrible place and see what remains of the old life can be found. My wife's great-grandfather, Sir Henry Holland, owed a great deal I think to that Unitarian circle. His father was Peter Holland, Surgeon, of Knutsford (the original of 'Cranford'), whose father-in-law was the Reverend W. Willets, Unitarian, who persuaded Priestley to get on with his oxygen work, and whose mother-in-law was Catherine Wedgwood, the great Josiah's favourite sister. There was much linkage between the Warrington, Manchester and Staffordshire Unitarians, and no doubt with other groups elsewhere. Perhaps all this has been written up, and I should like to find out. Some of the best intellectual life in the country went on in those circles—to which of course the Darwins belong—and it ought not to be kept obscured from history merely because the orthodox and sterile Church in those days kept it out of University and social prominence. Believe me, Yours sincerely, Walter M. Fletcher

In 1932, when invited to read a paper at the Johns Hopkins Medical History Club, I chose as my subject the Warrington Academy⁵, later, I sent a copy of the paper to Sir Walter, reminding him of his letter to Osler. His reply, written on March 27, 1933, a few weeks prior to his death, was characteristic.

I had utterly forgotten that letter of mine to Osler about the Warrington group, and I am really grateful to you for sending me a copy of it. It brings back very happy memories. I wonder how you came upon this? Did Osler put his

⁵ Fulton, J. F. The Warrington Academy (1757-1786) and Its Influence upon Medicine and Science, *Bull. Inst. Hist. Med.* 1: 50-80, 1933, in *Bull. Johns Hopkins Hosp.*, February 1933.

correspondence into the Library at McGill? That note to him must have had some relation to my finding him a copy of the first (4to) edition of Ferriar's *Bibliomania*. He told me he had looked in vain for this for a quarter of a century, I went with him and, I think, James MacKenzie to talk to Sir Alfred Keogh at the War Office about the disposal of heart cases during the War. I left W O in Trafalgar Square and walked up Charing Cross Road, and put my hand at once upon the *Bibliomania*, bound with some other pamphlets. I sent it to him in a suitable dress with a triumphant cry!

When I was half convalescent after pneumonia and empyema a year or two later, he came to my bedroom and left a parcel to be opened after he had gone, to cheer me up, as he said. This was another copy he had found and had put into a lovely whole binding with a suitable quotation written inside it from the *Philobiblon*. Happy, happy days when Osler was about! Things seem very dreary in comparison now.

This act was in keeping with one of Osler's favorite aphorisms, that "every book has its natural habitat," and nothing gave him greater personal pleasure than to fill a gap in the shelves of a fellow collector. He also stimulated an unending series of interns and junior students by the gift of some important early book. But for him all this was really bread on the water, for his friends, and his students, as they grew older, were never more pleased than when they could find a book to add to his collection.

Although Sir William gave books most liberally to his friends and although during his life he would loan anything from his library, six months prior to his death he sent a memorandum to McGill, stating, "Books are not to be lent or removed from the Library." This condition has been most embarrassing to his librarian, and it is so completely foreign to Osler's generous spirit that I have always suspected that he was unwell when he made the stipulation. One hopes that his trustees will have the wisdom, one day, to set it aside.

His humanism found further expression in his advice to students about general reading, for he felt that no man could have a well stocked mind who fed it with scientific literature alone. Plato, Rabelais and Shakespeare he considered as important to a medical man as Starling's "Physiology." He would have been delighted with the bright fantasy lately conceived by Frederick C. Irving, of Harvard, entitled "Aesculapius Inspects the Harvard Medical School"⁶. In an imaginative conversation with a member of the faculty, Aesculapius says

I realize that once a student embarks upon the pursuit of medicine he enters the most exacting novitiate there is—one which admits no opportunity for the further development of general culture. I therefore ask you if, realizing this, Harvard Medical School requires that its matriculates be versed in such studies as literature—both classic and modern—history, philosophy, and the fine arts, for those form the background for every educated man?

⁶ Irving, F. C. *Aesculapius Inspects the Harvard Medical School*, read before the Aesculapian Club, Jan 11, 1947, Privately printed [1947]

To this question, the reply is made

By no means, Aesculapius Harvard Medical School—and in this it differs not at all from others in this country—requires that every student who enters should have devoted in college the equivalent of one year to biology, chemistry, and physics

If a student who applies for admission to a medical school is familiar with the pre-Socratic philosophy, or if he can read Horace, Dante, or Montaigne in the original, or if he understands how the introduction of perspective and the illusion of distance altered the course of Italian painting, he had best be quiet about it lest the authorities suspect that while prowling about in the enthralling storehouse of the past he has stolen too much time from his scientific studies

This is indeed a great pity [says Aesculapius], for when your students go out into the world to practice they will encounter among their patients and other laymen a number of people of intelligence and education, all their time will not be spent with other doctors

Many have asked how Osler managed to acquire his broad general knowledge in the midst of his innumerable professional responsibilities, responsibilities which demanded that he keep abreast of current medical literature. The answer lies in his pragmatic philosophy, his way of life. "A Way of Life"⁷ was, in fact, the unpretentious title he gave to his intimate confession of faith before a group of students at Yale University in the spring of 1913, when, as Regius Professor of Medicine at Oxford, he had come to New Haven to deliver the Silliman Lectures on the evolution of modern medicine.

His philosophy was a simple one that may be epitomized in a sentence from Carlyle which Osler had chanced on in the summer of 1871 when, at the age of 23, he was much worried about his own future. "Our main business," Carlyle wrote, "is not to see what lies dimly at a distance but to do what lies clearly at hand." Of this, Osler said: "A commonplace sentiment enough, but it hit, and stuck, and helped, and was the starting point of a habit that has enabled me to utilize to the full, the single talent entrusted to me."

William Osler, as a student, thus disciplined himself into doing today's work today and never worrying about the future or the past—living, as he put it, in day-tight compartments. It was in this way that he was able to accomplish an astonishing amount of work and earn the time for the humanistic endeavors which were so important to him. During breakfast he would often jump up a half-dozen times to consult some reference work to settle a point that had come up in general conversation or in the course of perusing the morning paper. One of his pet tags, as he reached for a volume of the "Dictionary of National Biography," was "The flighty purpose never is o'ertook, Unless the deed go with it." By keeping his mind thus constantly on the alert, he piled up in his extraordinarily retentive memory a vast knowledge of art, literature and history. And it was

⁷ Osler, W. *A Way of Life*, London, Constable & Company, 1913

his ability to call on this knowledge readily, in public addresses or private conversation, that made his discourse so full of interest and inspiration

Osler's most signal recognition as a humanist came in 1918, when he was elected president of the Classical Association, a society made up of a large group of scholars from British universities and schools, whose object is "to promote the development and maintain the well-being of classical studies" The body was established in 1904, and its previous presidents had been such men as Lord Curzon, Prime Minister Asquith, Sir Archibald Geikie, Viscount Bryce and Gilbert Murray, Osler wrote a friend that every other year they had a common citizen, and that that was how he had happened to be elected However, when Murray nominated Sir William as his successor, he referred to him as a man

who is not only one of the most eminent physicians in the world, but represents in a peculiar way the learned physician who was one of the marked characters of the seventeenth and eighteenth centuries and stands for a type of culture which the Classical Association does not wish to see die out of the world⁸

Osler chose as a title for his presidential address the following year, "The Old Humanities and the New Science"⁹ The theme was well expressed by the phrase of Prof J A Stewart "No humane letters without natural science, and no natural science without humane letters" The choice of subject was a courageous one in view of the fact that it was being delivered in classical Oxford before a national body of classical scholars, but no one knew the pitfalls better than Osler or was more capable of dealing with them

As background for the address, he selected twenty volumes from the "Bibliotheca Prima" section of his library to be placed on display—each of them a milestone in the evolution of science and medicine from Hippocrates to Newton In addition to the books, he arranged an exhibit of early scientific apparatus, prevailing on R T Gunther, a science tutor at Oxford, to help him hunt out of obscure corners around the university the old astrolabes, orreries, telescopes, lenses and microscopes which were proof that Oxford had a glorious, if forgotten, past in experimental science Great interest was aroused by this exhibit, especially when Osler was on hand to tell the history and associations of the various instruments

The address itself was probably the most remarkable of his career The war had broken his heart His only son was gone, and the impact of the war and his own loss on his sensitive nature appears in many passages But he was able to take solace in the texts he knew and

⁸ Cushing, H, in introduction to Osler⁹

⁹ Osler, W The Old Humanities and the New Science, Boston, Houghton Mifflin Co., 1920

loved so well. In a world so lately torn and shattered by the scientific instruments of war, there was need, more than ever, of the leavening of the humanities. He proposed that Oxford set an example to the world by integrating science and the humanities in a new "honour school," in which the principles of philosophy would be dealt with in relation to the sciences and in relation to literature and general history, an approach which the young George Sarton was then advocating so warmly as the "new humanism." The science student

should go to the sources and in some way be taught the connection of Democritus with Dalton, of Archimedes with Kelvin, of Aristarchus with Newton, of Galen with John Hunter, and of Plato and Aristotle with them all. Science will take a totally different position in this country when the knowledge of its advances is the possession of all educated men.

The address was presented in the great medieval hall of the Divinity School at Oxford. The vice chancellor presided, and there was a large audience in colorful academic dress. Standing in the black oak pulpit in scarlet gown and cap, with the sun filtering through the ancient windows, Osler himself looked like a medieval figure. William Welch, who happened to be in Oxford at the time, wrote that "the charm and interest of the address and its cordial appreciation and reception by the audience all combined to make a scene of brilliancy and delight which I shall always carry in my memory."⁸ Welch was not alone in his enthusiastic reactions, for Sir Frederic Kenyon's comment was that "no one could hear it without being impressed with Osler's breadth of outlook, by his easy mastery of great tracts of literature and learning, by his all-embracing humanity in the widest sense of the term."⁸

It was Osler's last major address. I think he realized that it would be so, for he put the best he had into it, and an appropriate message it was for one about to leave the "flaming ramparts of this world." It summed up his philosophy regarding the inseparability of science from literature and learning, and it stands as a ringing valedictory to a lifework which earned him a place for all time in the ranks of the great humanist physicians.

And so he joined

the choir invisible
Of those immortal dead who live again
In minds made better by their presence live
In pulses stirred to generosity,
In deeds of daring rectitude, in scorn
For miserable aims that end with self,
In thoughts sublime that pierce the night like stars,
And with their mild persistence urge man's search
To vaster issues

PATHOGENESIS OF RENAL LESIONS IN BRIGHT'S DISEASE

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BETWEEN 1895 and 1914, Osler published a series of four papers¹ on the visceral manifestations of the erythema group of cutaneous diseases, pointing out, among other things, the frequency and severity of involvement of the kidneys in these conditions. In the three earlier papers,^{1a-c} written between 1895 and 1904, 29 examples of visceral manifestations in patients in "the erythema group" were reported. Fourteen of these had acute nephritis, and 5 of the 14 died of uremia. Of the 14 patients with nephritis, 13 had purpura.

As Osler well knew, this collection of cases contained examples of a number of different conditions, "certain of the purpuras, angio-neurotic oedema, peliosis rheumatica, exudative erythema." A study of Osler's case reports leads me to believe that of the 14 cases of nephritis, 1 (case 14) was quite possibly an example of periarteritis nodosa, whereas the disease in 2 (cases 19 and 26) would almost certainly now be diagnosed as disseminated lupus erythematosus and that in the remaining 11 as examples of Schonlein-Henoch syndrome (idiopathic nonthrombopenic purpura). It is clear from a perusal of the papers that Osler was deliberately grouping these various conditions because he sensed, early in his observations, and well before the date when anaphylaxis was first described, a common pathogenesis. By 1904 this concept of a common pathogenesis had advanced a considerable way, by 1914 it was fully established. The following quotations are relevant.

A criticism has been made on my previous papers that I had jumbled together a motley group of cases, some of purpura, some of angio-neurotic oedema, others of peliosis rheumatica, others again of exudative erythema. I did so on purpose, for I was seeking similarities not diversities.^{1c}

On the other hand the members of the erythema group have not all the same etiology, and, indeed, as is well known, the individual members have a very diverse etiology. It is not unlikely that the poison in itself, of whatever kind, is of less intrinsic importance than certain transient aspects of cell metabolism.^{1c}

Chronic angio-neurotic oedema, urticaria, and some forms of purpura are possible anaphylactic phenomena in persons sensitized for certain protein substances. Before long the anaphylactic key will unlock the mystery of these cases.^{1d}

1 Osler, W. (a) *Am J M Sc* **110** 629, 1895, (b) *Brit J Dermat* **12** 227, 1900, (c) *Am J M Sc* **127** 15, 1904, (d) *Brit M J* **1** 517, 1914.

I propose to attempt to follow Osler's example by grouping together, in this paper, a number of different conditions which may have a common or closely related pathogenesis. I refer to the various conditions which have one important factor in common, that of disorders of the small arteries and capillaries of the kidney, leading to the production of nephrosclerosis (Bright's disease). In doing so, I shall include some of the conditions studied by Osler but shall add to them other disorders known or suspected, to be related. This part of my paper is, in a sense, merely an extension of Osler's observations. I then propose to discuss the renal lesions developing in some cases of arterial hypertension and shall point out that, though of apparently different origin from those discussed in the earlier part of the paper, they are morphologically comparable, their similarity, indeed, being one of the major difficulties in the understanding of nephritis. I shall then briefly discuss the cause of these lesions associated with hypertension and their relation to the lesions in other forms of nephritis.

A few years ago, I suggested² that there were two types of nephritis in which the natural history of the disorder was so different as to justify their separate consideration. I also indicated that there were distinctive morphologic characteristics in these two types of nephritis. I referred to these forms as type 1 and type 2 nephritis. Type 1 nephritis typically has an acute onset with hematuria, following a week to ten days after an infection (usually of the upper respiratory tract with a hemolytic streptococcus). Complete recovery is the rule, but the disorder may run a rapidly progressive course to death from renal failure in six to twelve months, or it may become chronic, with persistent albuminuria. In the latter case renal failure with hypertension usually supervenes, often many years or decades later. The essentially vascular nature of the lesions in type 1 nephritis is reflected in the pathologic picture. In severe cases with death in the early stage, in addition to the changes in the glomeruli, acute necrosis of arterioles and capillaries may occur, in the long-standing, chronic cases the renal atrophy and fibrosis show a pronounced focal pattern, clearly related to the arterial blood supply. Type 2 nephritis, in which classification I include the condition frequently known as "lipid nephrosis," has a gradual onset, usually without hematuria and without any previous history of infection. Recovery is exceptional, the disorder usually running a continuous and progressive course, with heavy albumin content of the urine and more or less constant edema. If death does not occur from intercurrent infection in the early stage with severe edema, hypertension eventually develops, and the patient dies of renal failure, usually within two to ten years of the onset of edema. The course of the disease may, however, vary

2 Ellis, A. *Lancet* 1 1, 34 and 72, 1942

from a few months to twenty or thirty years. Complete recovery occasionally occurs, even when the disorder has been present for many years. In the early stage, histologic changes similar to those occurring in type 1 nephritis, but less intense in degree, may be present, or there may be any gradation from this picture to that of so-called lipid nephrosis, in which, except for tubular degeneration, morphologic changes are insignificant or lacking. In the later stages the kidneys present a glomerular lesion, characterized particularly by lobulation and "hyalinization" of the capillary tufts and by hyaline thickening of the basement membranes. The lesion is characteristically diffuse, all glomeruli being involved and all showing relatively the same stage and degree of change. In late stages of both type 1 and type 2 nephritis, but especially of type 1, the morphologic picture is complicated by added lesions resulting from the accompanying hypertension.³

It is now generally accepted that acute nephritis is a phenomenon of hypersensitivity or is dependent on some similar antigen-immune body reaction, this concept was advanced by Schick as long ago as 1907.⁴ It was developed especially by Longcope and his pupils,⁵ by Masugi,⁶ and by Swift and his associates Smadel and Farr.⁷ In cases of type 1 nephritis the common history of preceding infection affords clinical evidence for this view, in cases of type 2 nephritis such an association is not obvious, but this does not mean that it may not exist. I shall return to this point later. Irrespective of the question of etiology, this separation of two types of nephritis has been widely accepted as facilitating an understanding of the natural history of nephritis. It is especially helpful in the teaching of students and in determining the prognosis in individual cases.

In addition to the two types of classic nephritis, there are a number of conditions in which a nephritis similar to, and sometimes difficult to distinguish from, the classic forms may occur. In these conditions the associated nephritis occurs sufficiently often, or its mode of onset and course are sufficiently regular, to suggest that the nephritis has an intrinsic relation to the original disorder. I refer to the Schonlein-Henoch syndrome, rheumatic fever (though here the criterion of frequency does not apply), periarteritis nodosa, disseminated lupus

3 Wilson, C., and Byrom, F. B. *Quart J Med* **10** 65, 1941

4 Schick, B. *Jahrb f Kinderh* **65** 172, 1907

5 Longcope, W. T. *J Exper Med* **18** 678, 1913, *Am J M Sc* **152** 625, 1916, *Bull Johns Hopkins Hosp* **45** 335, 1929. Lukens, F. D. W., and Longcope, W. T. *J Exper Med* **53** 511, 1931

6 Masugi, M. *Beitrag z path Anat u z allg Path* **91** 82, 1933, *ibid* **92** 429, 1934, *Zentralbl f inn Med* **56** 417, 1935

7 Smadel, J. E. *J Exper Med* **64** 921, 1937, *ibid* **65** 541, 1937. Smadel, J. E., and Farr, L. E. *ibid* **65** 527, 1937. Swift, H. F., and Smadel, J. E. *ibid* **65** 557, 1937

erythematosis, subacute bacterial endocarditis (particularly in the bacteria-free stage) and amyloid disease

Five of these conditions, nephritis, Schonlein-Henoch syndrome, rheumatic fever, periarteritis nodosa and lupus erythematosis, have a further important common feature, an acute, focal, necrotizing lesion of arteries or arterioles, sometimes also involving capillaries. The lesion occurs consistently in some of these conditions, for example, periarteritis nodosa, but rarely in others, such as rheumatic fever. The morphologic characteristics of the necrotic lesions of blood vessels have a great similarity in the different diseases. Apart from the size of the vessel affected and the area of distribution, their features may be difficult or impossible to distinguish. It is dangerous to base a conclusion of similarity on morphologic changes alone, but in these conditions there are also similarities in certain clinical features and some evidence of a common pathogenesis. All five conditions may overlap the one with the other, and in all five, with the possible exception of lupus erythematosis, there is good ground for the belief that they are associated with an antigen-immune body reaction akin to anaphylaxis.

PERIARTERITIS NODOSA

The important observations of Rich and his associates Follis and Gregory⁸ brought new light to the etiology of this condition. Rich^{8a} reported the finding at autopsy of vascular lesions characteristic of periarteritis nodosa in the viscera of 5 patients who, shortly before death, had had hypersensitive reactions following therapeutic injections of foreign serum. Four of the patients had also received sulfonamide drugs, but the evidence indicated that in at least 2 of them the hypersensitive reaction was serum sickness, not drug hypersensitivity. The fifth patient had serum sickness without sulfonamide therapy, a biopsy specimen from a muscle showed vascular lesions typical of periarteritis nodosa. In another patient, who had had sulfathiazole prophylactically (but no serum), similar lesions were observed. A search of the records of the Johns Hopkins Hospital revealed only 1 case in which postmortem examination had been done on a patient with serum sickness, examination of sections showed periarteritis nodosa. Clark and Kaplan⁹ had previously noted arterial lesions of precisely the same character in 2 patients who had had serum sickness before death, sulfonamide drugs had not been given. In a second paper, Rich and Follis^{8b} reported an

8 (a) Rich, A. R. *Bull. Johns Hopkins Hosp.* **71** 128, 1942. (b) Rich, A. R., and Follis, R. H., Jr. *ibid.* **71** 375, 1942. (c) Rich, A. R., and Gregory, J. E. *ibid.* **72** 65, 1943.

9 Clark, E., and Kaplan, B. I. *Endocardial Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man*, *Arch. Path.* **24** 458 (Oct.) 1937.

additional instance of periarteritis nodosa following a hypersensitivity reaction during the prophylactic administration of sulfathiazole. Further, Rich and Gregory^{8c} described the experimental production of typical periarteritis nodosa by establishing in rabbits a condition analogous to serum sickness in man. Large amounts of horse serum (10 cc per kilogram of body weight) were used as the sensitizing dose, in 9 animals serum alone was given, and in 5 sulfadiazine was also administered. Periarteritis nodosa occurred in 12 of the 14 inoculated animals. Germane to this discussion is the fact that "acute diffuse glomerulonephritis" occurred in 10 of the 12 rabbits showing vascular lesions, and that "the nephritis had the histological characteristics of acute glomerulonephritis in man." The authors concluded that their experimental and clinical evidence showed that "widely different types of sensitizing antigens are capable of causing periarteritis nodosa in man."

The observations of Rich and his colleagues on the anaphylactic nature of periarteritis nodosa and the demonstration of acute diffuse glomerulonephritis in 10 of 14 rabbits sensitized with large doses of horse serum, and in 10 of 12 rabbits showing arterial lesions, must be given a central place, for periarteritis nodosa is an integrating link in the conditions under consideration.

SCHONLEIN-HENOCH SYNDROME, ACUTE NEPHRITIS, RHEUMATIC FEVER AND PERIARTERITIS NODOSA

Gairdner,¹⁰ in a careful study of the Schonlein-Henoch syndrome, presented evidence relating the syndrome to acute nephritis, rheumatic fever and periarteritis nodosa. He pointed out that the syndrome frequently coexists with nephritis, and occasionally with rheumatic fever, and that the necrotizing arteriolar lesions provide a suggestive pathologic link with periarteritis nodosa. Further, acute nephritis, periarteritis nodosa and rheumatic fever also show a tendency to coexist. In all four conditions there is evidence of hypersensitivity, sometimes bacterial and sometimes nonbacterial, as an etiologic factor. My own experience, gained chiefly from the study of nephritis, confirms Gairdner's observations. I have been impressed by the association of nephritis with the Schonlein-Henoch syndrome and with periarteritis nodosa. While acute nephritis is a rare complication of rheumatic fever, chronic rheumatic disease occurs sufficiently often in association with nephritis to suggest a connection between the two conditions. Gairdner pointed out that in all four conditions save rheumatic fever a vascular lesion is the dominant feature and that in rheumatic fever a generalized arteriolitis, which occurs in a proportion of cases, is with difficulty distinguished from periarteritis nodosa, as Aschoff himself first noticed in 1904.¹¹

10 Gairdner, D. *Quart J Med* **17** 95, 1948.

11 Aschoff, L. *Verhandl d deutsch path Gesellsch* **8** 46, 1904.

DISSEMINATED LUPUS ERYTHEMATOSUS

I have pointed out that a rereading of Osler's reports of instances of nephritis occurring in cases of the erythema group of cutaneous diseases^{11-c} suggests that at least 2 cases were examples of what is now called disseminated lupus erythematosus. It is to Baehr, Klemperer and Schiffrin¹² and to Klemperer, Pollack and Baehr¹³ that one is chiefly indebted for knowledge of the natural history and the pathologic anatomy of this condition. Renal lesions are a frequent manifestation in this disorder, Klemperer, Pollack and Baehr stated that they were specific, but from the description the lesions showed great similarity to those in certain examples of classic nephritis. The authors stated that the disease is a widespread disorder of collagen. In their clear, factual report on "Pathology of Disseminated Lupus Erythematosus,"¹³ they were careful to state that "speculations as to etiology are not germane to the purpose of this paper." But, in the course of their discussion, they did say

There are, however, other diseases in which widespread injury of collagen plays an outstanding role. Thus, rheumatic fever and generalized scleroderma demand comparison and differentiation. Moreover, the extensive vascular alterations in periarteritis nodosa and in accelerated arteriosclerosis, as well as the glomerular lesions in diffuse and focal glomerulonephritis, exhibit undoubted similarities which necessitate discussion.

The authors then proceeded to discuss the similarities and to minimize their significance because of the variations in the different disorders. Obviously, one cannot repeat here their arguments, which were prolonged and penetrating, but, in spite of the differences which they elaborated, there are undoubted similarities. Thus, in discussing the vascular lesions in disseminated lupus erythematosus and periarteritis nodosa, they stated

While the vascular lesion in both diseases may be differentiated (severity and localization), they are nevertheless fundamentally similar so far as primary damage of collagen underlies the definitive vascular alteration.

Again, in discussing the lesions of disseminated lupus erythematosus and of nephritis

The 'wire loops' seen in nephritis are tinctorially and configurately, as far as we can determine, identical with those found in lupus erythematosus.

It is apparent from these quotations that disseminated lupus erythematosus has certain similarities to the conditions previously discussed in this report, but these similarities are not so clearly defined as in the

12 Baehr, G., Klemperer, P., and Schiffrin, A. *Tr. A. Am. Physicians* 50: 139, 1935.

13 Klemperer, P., Pollack, A. D., and Baehr, G. *Pathology of Disseminated Lupus Erythematosus*, *Arch. Path.* 32: 569 (Oct.) 1941.

relation among the other members of the group. Further, though a hypersensitivity reaction has been suspected in cases of lupus erythematosus, I know of no evidence other than the occurrence of necrotic vascular lesions, the development of renal capillary lesions and the fact that the condition is apparently primarily a disorder of collagen which supports this hypothesis. My own experience with disseminated lupus erythematosus is not adequate to carry the discussion further.

SUBACUTE BACTERIAL ENDOCARDITIS

In this condition, a variety of lesions occur in the kidney, making the picture difficult of analysis. The commonest lesion is probably hemorrhage into the capsular space, with subsequent epithelization and fibrosis, as described by Russell¹⁴. There occur also multiple emboli, resulting in areas of focal nephritis. In addition to the focal lesions, diffuse nephritis, resembling the classic disease, may occur. As was pointed out by Libman,¹⁵ the nephritis usually occurs only in the bacteria-free stage, when some degree of immunity to the infecting organism has developed, suggesting again an antigen-immune body reaction.

AMYLOID DISEASE

Surprise may be expressed that I should include amyloid disease as a condition with which nephritis is associated, since amyloid disease of the kidney is normally regarded as a form of "nephrosis". I believe that this distinction of nephrosis and nephritis has been overemphasized and is largely artificial. As I have pointed out,² in my experience there is no justification for the distinction between nephritis and "lipid nephrosis". I am equally convinced that the genesis and mode of development of the pathologic process in "amyloid nephrosis" justifies the older association with nephritis, which was unwittingly made by Bright himself. Amyloid disease is now generally accepted as an antigen-immune body phenomenon. For this opinion there is convincing evidence, both experimental and from the natural history of the disease. Amyloid disease is, however, obviously not an example of the "anaphylactic" type of antigen-immune body reaction, typically presenting in serum sickness, here, one has to do with a reaction of insidious onset and slowly developing tempo. It is of interest that the slowly developing reaction leads to morphologic changes in the kidney which have a close resemblance to type 2 nephritis. At times it is only by specific staining

14 Russell, D. S. A Classification of Bright's Disease, Medical Research Council, Special Report Series, no. 142, London, His Majesty's Stationery Office, 1929.

15 Libman, E., cited by Fishberg, A. M. Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 426.

methods that amyloid disease of the kidney can be distinguished from type 2 nephritis. Similarly, the renal lesion in disseminated lupus erythematosus, as described by Klemperer, Pollack and Baehr,¹³ bears a close resemblance to the lesion in those examples of type 2 nephritis in which thickening and hyalinization of the basement membrane is the dominant lesion. Further, in diffuse nephritis complicating the bacteria-free stage of subacute bacterial endocarditis, or accompanying chronic rheumatic disease, the renal lesion often resembles that of type 2 nephritis.

Reviewing the whole group of conditions with which nephritis is associated, one is led to the conclusion that the response of the kidney to antigen-immune body reactions may be one of two distinct kinds. The first is an acute anaphylactic response, from which recovery is the rule, in fatal cases vascular necrosis is seen to be a prominent feature. The second is an insidious and usually progressive response of less intensity, in which vascular necrosis is minimal, in this type of response, the disorder of glomerular permeability is conspicuous and prolonged, and a distinctive type of structural alteration develops. While the reaction usually conforms to one or the other of these patterns, occasionally both types of response are encountered in the same case.

RENAL LESIONS ACCOMPANYING HYPERTENSION

I turn now to a disorder of a different kind, in which damage to small arteries and capillaries of the kidneys leads to a morphologic picture often indistinguishable from that of nephritis. I refer to the changes occurring in the kidney as a result of hypertension, which reach their maximum expression in "malignant hypertension." The subject is discussed at length in my Croonian lectures,² in which the development of knowledge of the lesions of the kidney arising from hypertension, culminating in their experimental production in animals, is traced. Here it is necessary only to emphasize certain similarities between the lesions and those already discussed. The most striking of these similarities is the character of the acute lesions occurring in the arterioles. In spite of their different causation, these acute vascular lesions are essentially similar in "malignant hypertension," in severe type 1 nephritis, in periarteritis nodosa, in the Schonlein-Henoch syndrome and in rheumatic fever when they occur in that condition. The morphologic features of these acute arterial lesions vary considerably, but the essential process is apparently similar in all. In my experience, the commonest demonstrable change is swelling of the so-called ground substance of the wall of the vessel. It is best seen in the subendothelial layer of the intima, where it often leads to separation of the endothelium from the elastic interna, with resulting narrowing, or even complete, obliteration of the lumen, subsequently, the homogeneously swollen

portion of the intima may become organized, giving rise to so-called, but misnamed, *endarteritis fibrosa*. In the more severely affected vessels necrosis occurs and may involve all coats, leading to their disruption. The process is best seen in *periarteritis nodosa*, in which the vessels are large. The destruction may be so severe as to suggest release of a lytic substance.

The similarity of the lesions in the kidney arising from the nephritic process, on the one hand, and from hypertension, on the other, and affecting both the glomeruli and the vessels, has been one of the major causes of confusion in interpreting the histologic pathology of nephritis. The difficulty is complicated by the fact that in the chronic stages of nephritis, lesions resulting from hypertensive vascular disease may be superimposed on the lesions of the original nephritis. The problem has been discussed by Wilson and Byrom,³ who, as a result of their differentiation of the two types of lesions, advanced the concept of a "vicious circle" in the pathogenesis of the renal lesions. As one becomes more closely acquainted with the natural history of nephritis in both its clinical and its histologic development, one appreciates how much of the confusion which has surrounded the subject has arisen from the combination of these two types of renal vascular damage—the "anaphylactic" and the hypertensive. "Malignant hypertension" with *periarteritis nodosa*-like lesions of the larger renal vessels may be almost indistinguishable from *periarteritis nodosa* with terminal malignant hypertension resulting from lesions of the renal arteries. The separation may indeed be impossible unless one has information about the early stage of the disease. But the problem is most evident in the differentiation of malignant hypertension and chronic nephritis with malignant termination—the traditional problem of "chronic interstitial nephritis." Only a careful study of the natural history of nephritis, which gives a longitudinal instead of a transverse section of the disease process, will lead to the true interpretation.

In spite of the similarity of the renal lesions in the conditions previously discussed and in malignant hypertension, there is no obvious indication of a common cause. In the former the lesions are thought to be anaphylactic in origin, and comparable to the acute necrotic vascular lesions seen in the Arthus phenomenon. In malignant hypertension there is nothing to suggest hypersensitivity, here one must look for another cause.

Wilson and Byrom³ stated that as a result of their observations on experimental hypertension in rats, they considered the lesions occurring in those circumstances a direct result of the hypertension. Goldblatt¹⁶ disputed this view, holding that a second, unknown, humoral, factor, possibly associated with renal failure, was responsible. The pros and

16 Goldblatt, H. J. *Exper. Med.* **67** 809, 1938, *Physiol. Rev.* **27** 120, 1947

cons of the discussion may be found in a recent paper by Byrom and Dodson¹⁷ I agree with them that Goldblatt's arguments are not valid. In the same paper, Byrom and Dodson reported the experimental production in rats of "typical acute necrotising arteritis" of the kidney, produced by "brief artificial overdilation of the arterial tree". This was brought about by repeated forcible injection with a syringe of Ringer's solution into the left common carotid artery. The authors concluded:

This experiment shows that sudden brief rises in intra-arterial tension can directly cause typical fibrinoid arterial necrosis in a normal animal and that the smaller arteries of the kidney are selectively vulnerable—the arterial muscle giving way suddenly and locally under the strain and provoking a vigorous attempt at repair.

In the course of the experiments, Byrom and Dodson noticed that there was blanching of the renal cortex immediately after the injection and that after several injections focal pallor of the cortex persisted. The authors appreciated the significance of the observation but discounted its importance, as they considered the vasoconstriction too transient to explain the vascular necrosis, and concluded, therefore, that it was due to overstretching. But the persistence of focal cortical blanching after the increased vascular tension had disappeared suggests a secondary mechanism, and the fact that subcapsular pallor was still present three days later, after death, suggests that the secondary mechanism had persisted. While it is conceivable that mechanical stress alone might produce death of the wall of the vessel, I consider it more likely that the observed vasoconstriction following the injection may have resulted in a diversion of blood from some parts of the vascular tree, the cause of necrosis being acute ischemia rather than mechanical stress.

I have so far discussed the pathogenesis of renal lesions, first, in a variety of conditions in which nephritis seems to occur as a manifestation of an antigen-immune body reaction, and, second, in hypertension. Although vascular damage is an essential feature in both types of disorder, the mechanism of its production is not adequately explained in either. Indeed, the explanation will not be forthcoming until more is known about the functional disturbance which precedes the organic lesion. It may be appropriate, at this point, to draw attention to another cause of nephritis. From early times, clinicians have been impressed by the sudden and rapid onset of acute nephritis after exposure to cold, wetting and immersion. The causative mechanism is not known, but the most plausible explanation is that a severe reflex vasoconstriction leads to renal ischemia. Is there, perhaps, the suggestion here of a common denominator which may apply to all the conditions under discussion,

17 Byrom, F. B., and Dodson, L. F. *J. Path. & Bact.* 60: 357, 1948.

namely, vasoconstriction leading to acute ischemia, with resultant damage to arterioles and capillaries? The work of Trueta, Barclay, Daniel, Franklin and Prichard¹⁸ revealed a mechanism through which such vasoconstriction and renal ischemia might be brought about. These workers showed that an alternative intrarenal circulation, under nervous control and in which large areas of the renal cortex may be by-passed, occurs in animals and is probably present in man. Such a mechanism could provide a common pathogenesis of all the conditions described in this paper. There is, I must emphasize, no direct evidence to support this suggestion. No indication exists that such a mechanism operates in anaphylaxis, in hypertension or in chilling of the body surface. But, to me, so revolutionary is the fact, revealed by Trueta and his associates, of the occurrence under nervous stimuli of changes in the caliber of main vessels, associated with a variable by-pass regulating the site and extent of capillary activity, that it seems to demand a reconsideration of the whole concept of the physiology and pathology of the kidney. However, my purpose is merely to group together a number of conditions with certain features in common. I am seeking, in the words of Osler, "similarities not diversities," in the hope that one day the key will be found to unlock the mysteries of these conditions, with which the names of so many of our great physicians, including him whom we honor in this memorial number, are associated.

37 Saint Giles's

18 Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L. - *Studies of the Renal Circulation*, Oxford, Basil Blackwell & Mott, Ltd., 1947.

POSTHUMOUS TRIBUTES TO SIR WILLIAM OSLER

E ROSENCRANTZ, M D
SAN FRANCISCO

All of him that we value here
Wakes on the morn of his hundredth year

“**E**VERY gift of the gods was his He was one of nature’s chosen” So wrote the late Fielding Garrison of Osler. It is almost thirty years since he died, and his eminence as a teacher and physician has not waned. Indeed, the years have added to his glory. No one has in any way taken his place as “the young man’s friend” and as “the world’s best doctor.”

Who can ever truly estimate the greatness of such a man? His fame lies not only in his achievement as a physician whose judgment in all things medical was outstanding, in his rich knowledge of biblical lore and in his remarkable learning of the Greek and Latin writers and his familiarity with philosophy and literature throughout the centuries, but in something greater still—his broad culture, combined with a kindred spirit toward all things, great and small, he thus taught and brought out the best in all mankind.

His popularity was, and still is, as great in England as in America. This international regard for him is indeed a striking manifestation of the esteem in which he was held. Seldom has any man attained the appreciation of his fellow citizens within his lifetime as did Osler.

One may obtain some perception of the man from his own writings and from what has been written about him. The many honors conferred on Osler during his lifetime have been given in careful detail by Cushing,¹ in his incomparable biography. An effort has been made in the present paper to tell succinctly of the posthumous tributes to him, with pen or otherwise, they range into thousands. In a short article they cannot all be enumerated and described, so for the sake of simplicity they have been classified.

From the Department of the History of Medicine and Bibliography, University of California Medical School

1 Cushing, H. The Life of Sir William Osler, Oxford, Clarendon Press, 1926

MEMORIAL SERVICES

- A Christ Church Cathedral (Funeral), Oxford, England, Jan 1, 1920¹
- B St Paul's Church, Baltimore, Jan 1, 1920, address by Rev H. P Almon Abbott²
- C St James's Cathedral, Toronto, Canada, Jan 11, 1920³
- D Christ Church Cathedral, Montreal, Canada, Feb 1, 1920⁴

MEMORIAL MEETINGS

- A Medical and Chirurgical Faculty and Book and Journal Club, Baltimore, Jan 9, 1920⁵
- B New York Academy of Medicine, New York, Feb 28, 1920⁶
- C Johns Hopkins University, Baltimore, March 22, 1920⁷
- D Simcoe County Medical Association, Bond Head, Ontario, Canada, Sept 20, 1930⁸

A Medical and Chirurgical Faculty and Book and Journal Club

The Osler Memorial Meeting of the faculty was held jointly with the Book and Journal Club at the home of the Club on Jan 13, 1920 After a resolution on Osler's death, Dr Harry Friedenwald told of the saintly qualities of Osler, his interest in books and libraries was related by Dr John Ruhrah, an address was given by Francis Packard on Osler's services to medical history, and Dr William S Thayer spoke on "Osler"

B New York Academy of Medicine

At a special meeting, Dr George David Stewart presided and made the introductory remarks Sir William's great friend, Dr Francis J Shepherd, of Montreal, spoke of Osler as a student at McGill, emphasizing how the young men loved and revered him He told how Osler's wisdom had harmonized the various factions in the medical world and described his scientific methods in the veterinary school, his great success as the first pathologist of the Montreal General Hospital and how his enthusiasm infected others Dr Thomas McCrae gave a résumé of Osler's life, dwelling on his various activities in Canada, the United States and England In referring to Osler's devotion to Linacre, Harvey and Sydenham, he added what is so truly felt that Osler combined the qualities of all three The tribute to Osler as a man of letters was given by Dr Edward C Streeter, of Boston He stressed the literary acumen and the unique combination of qualities which accounted for Osler's distinguished place in the world

2 The Osler Memorial Service, St Paul's Church, Baltimore, Jan 1, 1920, Baltimore, privately printed, 1920

3 Osler Memorial Service, *Canad J Med & Surg* **47** 120-130, 1920

4 Memorial Services, Christ Church Cathedral, Montreal, Feb 1, 1920, *Brit M J* **1** 205, 1920

5 Osler Memorial Meeting of the Medical and Chirurgical Faculty and the Book and Journal Club, *Bull M & Chir Fac Maryland*, **12** 60-78, 1920

6 Memorial meeting of the New York Academy of Medicine, New York *M J* **111** 920-924, 1920

7 Osler Memorial Meeting at Johns Hopkins University, *Johns Hopkins Alumni Mag* **9** 296-311, 1921

8 Gwyn, N B Simcoe County Memorial Meeting at Bond Head, *Canad M A J* **23** 704-705, 1930

C Johns Hopkins University

A memorial meeting was held on March 22, 1920, at the institution where Osler had worked for sixteen years. Henry Van Dyke paid tribute to Osler's remarkable personality and, from Tennyson's "In Memoriam," quoted the lines so appropriate to Osler—"Wearing all that weight of learning lightly like a flower."

Dr William H. Welch, so long Osler's confrere, stressed the sound medical organization of Osler's service at Johns Hopkins Hospital, and his methods and merits as a clinical teacher and as a public-spirited citizen. Dr William S. Thayer's words bared the heartstrings of a beloved disciple and colleague, and Mrs. Edith G. Reid expressed her sentiments in "Osler as Giver of Life."

D Simcoe County Medical Association

Under the auspices of the Simcoe County Medical Association, a memorial service was held at Bond Head, where Osler was born, at an afternoon session of the district medical meeting of the Ontario Medical Association, amid many relatives, family friends and members of the medical profession in the vicinity. In Trinity Church, where his father had been rector for many years and where Osler was baptized, a simple church service was conducted by the Lord Bishop of Toronto. Dr. Cummings of Bond Head presented, on behalf of the medical association, a stained glass window and a brass tablet. Dr. Norman Gwyn of Toronto, Osler's nephew, gave the address of the day, and the granddaughter of Sir Edmund Osler unveiled both tributes.

OBITUARIES AND EDITORIALS

After the death of Osler, innumerable obituaries, articles of appreciation and sentiments extolling his influence appeared in journals far and wide, lay and medical. In the Abbott memorial volume,⁹ the bibliography is given. Plans have been made to bring the list up to date in the near future. Many editorials have been dedicated to his influence and his deep interest in medicine, including his contributions to pathology, and stirring tributes have been paid to him as a man and as a physician.

MEMORIAL VOLUMES AND ISSUES OF JOURNALS

- A *Bulletin of the Medical and Chirurgical Faculty, Maryland*⁵
- B *Bulletin of the International Association of Medical Museums*⁹
- C *Canadian Medical Association Journal*¹⁰
- D *Canadian Journal of Medicine and Surgery*¹¹
- E *Tufts College Medical Journal*¹²

9 Abbott, M. E. Sir William Osler Memorial Number. Appreciations and Reminiscences, Bulletin 9, International Association of Medical Museums. Toronto, Murray Printing Co., Limited, 1926, pp. 607-626.

10 Canad. M. A. J., Special Osler Anniversary Number, July, 1920.

11 Canad. J. Med. & Surg. 47: 105-164, 1920.

12 Tufts Coll. M. J. 5: 2-24, 1939.

A *Bulletin of the Medical and Chirurgical Faculty, Maryland*

In the Osler memorial issue of the bulletin are recorded the details of the memorial meeting mentioned. The resolution on Osler's death is given in detail.

B *Bulletin of the International Association of Medical Museums*

For an outpouring of appreciation of Osler, one turns to the memorial volume edited by Maude E. Abbott. This fine book, dedicated in loving memory to Sir William Osler, is composed of articles written by devoted friends, confreres and former students. Editorials are dedicated to his influence in medicine and to his contributions to pathology, and moving tributes, to Osler as a citizen and practitioner. The general articles deal with Osler's work as clinician, great teacher and bibliophile, in the biographic subdivisions are covered his early years and the Montreal, Philadelphia, Baltimore and Oxford periods. Appended to each chronologic section are groups of delightful articles, written by those who knew him and had contact with him during those years. Added are a classified bibliography of his writings and a list of writings about him (described later in the present paper). Illustrations of memorials, also described here, add further interest to the extensive collection.

C *Canadian Medical Association Journal*

In the memorial number is printed in full the sermon preached at the memorial services held at Christ Church Cathedral in Montreal. There are also sixteen other articles, written by friends and former students, depicting his years in Canada, Philadelphia and Baltimore. His last days are eloquently described by his old friend, Dr. George Adam.

D *Canadian Journal of Medicine and Surgery*

An editorial by Irving H. Cameron brings out the influence of James Bovell on Osler, and a striking comparison is made with the great Boerhaave, of Leyden. The address, by Rev. T. C. S. Macklen, at the memorial services at St. James's Cathedral, Toronto, is reprinted in its entirety. Dr. Lewellys F. Barker relates much about the busy life in Baltimore, the relations with other physicians and consultation work, the activities with the Book and Journal Club, which Osler started, his enthusiasm for public work, his helpfulness to the nursing school, and his unceasing regard at all times for the students.

His years at Montreal are described by his great friend and associate, Dr. Francis J. Shepherd, and Dr. Alexander McPhedran reviews his influence on medical education in the United States. The genius as a teacher is recalled by Dr. Harold C. Parsons. Dr. C. K. Clarke truly states that Osler's name is one of the greatest in medicine that the world has ever known. From his nephew, Dr. Norman B. Gwyn, one learns about the fine home influences that went to make him the rare man he was. Dr. Helen MacMurchy, who was a graduate student at Johns Hopkins in the early days, gives a fascinating account of the famous Thursday morning clinic.

E *Tufts College Medical Journal*

The March 1939 number of the journal is called "The Osler Edition." Both Dr. Joseph Pratt and Dr. Fred W. Thyng give charming pictures of Osler, and an interesting account of a day at Osler's clinic is furnished by Dr. Edward N. Cartnick. Dr. Lenard Klein gives a survey of the summer work done by the Osler society of that institution.

BIOGRAPHIC MATERIAL

Complete Books

A Cushing, Harvey Life of Sir William Osler¹

B Reid, Edith Gittings The Great Physician A Short Life of Sir William Osler¹³

A "Life of Sir William Osler"

Cushing's biography of Sir William Osler is considered the greatest, and is certainly the most comprehensive, ever written about any physician. It is a masterpiece of English literature. The author has described, in amazing detail and with great charm, Osler's growth and development, his achievements and the underlying qualities of his character. The years as a schoolboy, student and teacher, his great love for the medical profession, his influence on all who came within his reach, the extraordinary number of contributions to medical science and literature, and the unceasing kindness to all are so wonderfully unfolded that one closes the volumes reluctantly, only to return to them again and again. The measure of the success of the biography is illustrated strikingly in the profound effect it has had on those who never even knew Osler, among the laity as well as in the profession. One recalls the enthusiasm of Elmer Smith, an attorney in Chicago, who, after reading the volumes, became an Osler enthusiast and, for the remainder of his life, collected the literary writings of Osler. Smith published two booklets,¹⁴ expressing admirably the profound impression the biography made on him. Cushing was awarded the Pulitzer Prize for the biography in 1926.¹⁵

B "The Great Physician"

In this brief account, Edith Gittings Reid, a friend of the Oslers, reaches her objective of bringing forth the essential facts and fine qualities of the life of Osler. Her little daughter and Osler's son, Revere, were playmates, and Osler frequently visited her home, thus enabling her to portray another unusual side of his nature—his genuine love of and joy in children. The volume is a remarkable picture of Osler through the eyes of a sensitive layman.

Sketches

A Addison, Agnes Portraits in the University of Pennsylvania¹⁶

B *British Medical Journal*¹⁷

C Castiglioni, A History of Medicine¹⁸

13 Reid, E. G. The Great Physician. A Short Life of Sir William Osler, New York, Oxford University Press, 1931.

14 Smith, E. A. Sir William Osler as Seen by a Layman, Chicago, privately printed, 1931, The Impress of Books upon Life, Chicago, privately printed, 1943.

15 Fulton, J. F. Harvey Cushing, Springfield, Ill., Charles C. Thomas, Publisher, 1946, p. 463.

16 Addison, A. Portraits in the University of Pennsylvania, Philadelphia, University of Pennsylvania Press, 1940, pp. 39 and 40.

17 William Osler. A Short Biography and Some Tributes to His Memory, Brit. M. J. 1:1-33, 1920, also printed as a brochure.

18 Castiglioni, A. History of Medicine, translated from the Italian and edited by E. B. Krumbhaar, New York, Alfred A. Knopf, Inc., 1941, pp. 822-824.

- D Garrison, F H Introduction to the History of Medicine ¹⁹
- E Kagan, S R Leaders of Medicine Biographical Sketches of Outstanding American and European Physicians ²⁰
- F Lambert, S W, and Goodwin, G M Medical Leaders from Hippocrates to Osler ²¹
- G Lambert, S W, and Goodwin, G M Minute Men of Life The Story of the Great Leaders in Medicine from Hippocrates Down to the Present Day ²²
- H MacDonald, Adrian Canadian Portraits ²³
- I Morley, Christopher Modern Essays for Schools, Selected by Christopher Morley ²⁴
- J Moulton, F R, and Schifferes, J J The Autobiography of Science ²⁵
- K Newman, G William Osler A Physician of Two Continents ²⁶
- L Sherman, S William Osler, the High Calling of Medicine ²⁷

The admiration of a widely varied group of persons has prompted them to express their equally varied feelings and thoughts, inspired either by personal association or by indirect influence through Osler's writings or those about him. The sketches differ in length and detail.

Appreciations and Reminiscences

Still another group of writings in praise of Osler is composed of the almost countless articles in medical and lay journals. The expressions of admiration seem to cover every phase of Osler's life and add to our knowledge of the scope of his various activities in all fields of clinical medicine. Plans have been made to publish the bibliography of this enormous amount of material.

¹⁹ Garrison, F H Introduction to the History of Medicine, Philadelphia, W B Saunders Company, 1929, pp 630-632

²⁰ Kagan, S R Leaders of Medicine Biographical Sketches of Outstanding American and European Physicians, Boston, The Medico-Historical Press, 1941, pp 96-125

²¹ Lambert, S W, and Goodwin, G M Medical Leaders from Hippocrates to Osler, Indianapolis, Bobbs-Merrill Company, 1929, pp 319-331

²² Lambert, S W, and Goodwin, G M Minute Men of Life The Story of the Great Leaders in Medicine from Hippocrates Down to the Present Day, New York, Grosset & Dunlap, 1929, pp 311-331

²³ MacDonald, A Canadian Portraits, Toronto, Ryerson Press, 1925, pp 192-208

²⁴ Morley, C Modern Essays for Schools, Selected by Christopher Morley, New York, Harcourt, Brace & Company, 1921, pp 129-144

²⁵ Moulton, F R, and Schifferes, J J The Autobiography of Science, Garden City, N Y, Doubleday, Doran & Company, Inc, 1945, pp 605-613

²⁶ Newman, G William Osler A Physician of Two Continents, in Interpreters of Nature, New York, Oxford University Press, 1927, pp 229-247

²⁷ Sherman, S William Osler, the High Calling of Medicine, in Critical Woodcuts, New York, Charles Scribner's Sons, 1926, p 227

Autobiographies and Biographies with Extensive Reference to Osler

Among the numerous autobiographies and biographies, primarily of medical personalities, that have appeared during the last thirty years, there are many and extensive references to Osler. The accounts give valuable information about Osler's work and influence as a teacher, and about his wonderful amenities. The authors relate, in laudatory terms, his unparalleled charm and the great merits that have placed him among the "saints of humanity." A list of the books is to be published in a bibliography of writings about Osler.

ORATIONS AND LECTURES

A Osler Lecture, Vancouver Medical Association

B Osler Memorial Oration, Canadian Medical Association

C Osler Memorial Lectureship, Osler Memorial Association of Los Angeles

A Vancouver Medical Association

The Osler Lecture was inaugurated in 1921 at the suggestion of the president of the association, Dr F Brodie. Because of Osler's interest in the association and its library, an annual lecture was established as a permanent memorial to him. To each speaker so honored there is presented a bronze medal, after the gold one used at Oxford, on which is a replica of the Osler plaque, made by F Vernon in Paris in 1903. On the reverse side are inscribed the speaker's name and the quotation "Let us now praise famous men and our fathers that begat us." Names of the yearly recipients of the medal and the titles of their dissertations are

1921 W D Keith	"Sir William Osler, Physician and Teacher"
1922 J M Pearson	"The Style of Writing Exemplified by Osler"
1923 G Gordon	"Our Library" (History of Medicine)
1924 B D Gillies	"Recent Advances in Liver Function"
1925 F J Brodie	"Aphasia"
1926 E D Gardner	"Thymus"
1927 G E Seldon	"Musical Education"
1928 C H Vrooman	"Development of Our Knowledge Concerning Tuberculosis"
1929 H M Cunningham	"Ourselves (Retaining the Art of Medicine)"
1930 J J Mason	"A Study of a Personal Series of Hysterectomies and Myomectomies"
1931 R E McKechnie	"Reminiscences of Forty Years' Practice"
1932 F P Patterson	"Orthopedics"
1933 Glen Campbell	"The Eye"
1934 J G McKay	"Psychiatry"
1935 Wallace Wilson	"Goitre and the Background of Its Ancient History"
1936 A W Hunter	"Glances into Urology of the Past and Present"
1937 W A Whitlaw	"Gastric Ulcer"
1938 L H Appleby	"Quo Vadis Medicine?"
1939 J H McDermot	"The Layman and the Doctors"
1940 No lecture	
1941 G F Strong	"Some Observations on Coronary Artery Heart Disease"
1942 No lecture	
1943 D E H Cleveland	"The Fear of the Skin"
1944 T H Lennie	"Goitre"
1945 Howard Spohn	"The Employment of Leisure"
1946 A L Lynch	"Sir William Osler and Some of His Contemporaries"
1947 Bede J Harrison	"Medicine and Some Orthodoxies"
1948 Murray Blair	"A Priest of Lucina (William Smellie)"

B Canadian Medical Association

The inauguration of a triennial address, established in honor of the group's most distinguished citizen, as well as physician, was held at the annual meeting of the association on June 20, 1929 in Montreal, the city where Osler had spent

twelve years of his medical life, and where the foundation of his remarkable medical career was laid.²⁸ His friend of many years, Dr Francis J Shepherd, was chosen to give the first Osler Oration. Because he died before the meeting, his paper was read by Dr H T Lafleur, Osler's first resident at Johns Hopkins. Coincident with the occasion was Osler Day, an event of deep historical significance in the annals of medical affairs in Montreal. It was then that the magnificent Osler Library at the McGill University Medical School was opened to the public for inspection. The orations are not always presented in Canada. Twice they were given at joint meetings of the Canadian Medical Association and the American Medical Association at Atlantic City, N J. On those occasions, Dr Francis R Packard and Dr Lewellys F Barker read the papers. Various distinguished physicians have presented the orations:

1929 Francis J Sheperd	"The Osler Oration" (read by Dr H T Lafleur)
1932 Francis R Packard	"William Osler—The Men and Institutions with Which He Was Associated in Philadelphia"
1935 Lewellys F Barker	"Osler in America, with Special Reference to His Baltimore Period"
1938 Sir Humphrey Rolleston	"Sir William Osler, Bt, M D " I The Last Phase II His Influence on Medicine as a Whole
1942 Charles D Parfitt	"Osler's Influence in the War Against Tuberculosis"
1947 John McMichael	"Osler The Textbook and Education in Medicine"

In 1939 an Osler Hour was part of the annual meeting of the association. Jonathan C Meakins spoke on "Typhoid Fever in the 1890's and the 1930's", A H Gordon, on "Acute Endocarditis", Duncan Graham, on "Erythema—Polycythaemia Rubra Vera," and J Hepburn, on "Aortic Syphilis."

C Osler Memorial Association of Los Angeles

The organization was established about 1920 by a group of physicians in the vicinity of Los Angeles. The first lecture, given by Dr J T Finney in 1921, was "A Personal Appreciation of Sir William Osler." The association was short-lived.

BIBLIOGRAPHIES

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- B Abbott, Maude E. *Classified Bibliography of Sir William Osler's Publications with Annotations (1869-1919)* ⁹
- C Abbott, Maude E. *Classified and Annotated Bibliography of Sir William Osler's Publications (Based on the Chronological Bibliography by Minnie Wright Blogg)* ³⁰
- D Blogg, Minnie Wright. *Bibliography of Sir William Osler* ³¹

²⁸ The Osler Memorial Celebration, *Canad M A J* **21** 129-139, 1929.

²⁹ Abbott, M E. *Classified Bibliography of Sir William Osler's Canadian Period (1868-1885)*, Special Osler Memorial Number, *Canad M A J*, 1920, pp 103-123.

³⁰ Abbott, M E. *Classified and Annotated Bibliography of Sir William Osler's Publications (Based on the Chronological Bibliography by Minnie Wright Blogg)*, ed 2, Montreal, The Medical Museum, McGill University, 1939.

³¹ Blogg, M W. *Bibliography of Sir William Osler*, *Bull Johns Hopkins Hosp* **30** 219-233, 1919.

E Blogg, Minnie Wright Bibliography of the Writings of Sir William Osler ³²

F White, William Osleriana Since 1926 A Bibliography of Writings about Sir William Osler ³³

G White, William Bibliography More Osleriana, Addenda and Corrigenda to A Bibliography of Sir William Osler ³⁴

A, B, C The Abbott Bibliographies

A bibliography of Osler's publications in the years 1868 to 1885, classified by Maude E Abbott and based on the chronologic list by Minnie Wright Blogg, was published in the Osler memorial issue of the *Canadian Medical Association Journal* ²⁹ In the Osler memorial volume, ⁹ Dr Abbott completed the classified list, including all of Osler's publications, with annotations, later, the bibliography was reprinted separately ³⁰ It is a colossal achievement, and one that is invaluable to the student or collector interested in Osler

D, E The Blogg Bibliographies

On the occasion of Osler's seventieth birthday, July 12, 1919, the *Bulletin of the Johns Hopkins Hospital* for that month was dedicated to him, in it there appeared a bibliography of his writings prepared by Minnie Wright Blogg, ³¹ which gave Osler a great deal of pleasure He was deeply touched and appreciative, for the compilation represented great effort, inspired by devotion, it was the first time his writings had been gathered together Later the list was enlarged and published in book form ³² It is indispensable to the collector of Osler's writings because of the chronologic arrangement

F, G The White Bibliographies

William White, a student of English literature and a great admirer of Osler, although they never met, has published several papers about him Among them are two bibliographies, which cover articles both by and about Osler

BOOKS AND POEMS DEDICATED TO OSLER

Books

A Barker, L F Time and the Physician, Autobiography ³⁵

B Langstaff, J B Doctor Bard of Hyde Park The Famous Physician of Revolutionary Times, the Man Who Saved Washington's Life ³⁶

³² Blogg, M W Bibliography of the Writings of Sir William Osler, Bart, M D, F R S, Regius Professor of Medicine in the University of Oxford, Baltimore, Lord Baltimore Press, 1921

³³ White, W Osleriana Since 1926 A Bibliography of Writings about Sir William Osler, Bull M Library A 28 189-197, 1940

³⁴ White, W Bibliography More Osleriana, Addenda and Corrigenda to a Bibliography of Sir William Osler, Bull M Library A 30 157-160, 1942

³⁵ Barker, L F Time and the Physician, Autobiography, New York, G P Putnam's Sons, 1942

³⁶ Langstaff, J B Doctor Bard of Hyde Park The Famous Physician of Revolutionary Times, the Man Who Saved Washington's Life, New York, E P Dutton & Co, Inc, 1942

- C Lighthall, W D Person of Evolution The Outer Consciousness, the Outer Knowledge, the Directive Power, Studies of Instinct as Contributions to a Philosophy of Evolution ³⁷
- D Osborne, Marian The Song of Israfel and Other Poems ³⁸
- E Riesman, D History of the Interurban Club ³⁹
- F Thayer, W S Osler and Other Papers ⁴⁰

Poems

- A Emmons, E To Sir William Osler ⁴¹
- B Hoffman, F L Sir William Osler (in Memoriam) ⁴²
- C Nimeh, William The Mission of the Physician ⁴³
- D Osborne, Marian William Osler ⁴⁴
- E Osborne, Marian The Healer ⁴⁴
- F Osborne, Marian Dedication Sonnet to Sir William Osler ⁴⁵
- G Osborne, Marian William Osler A Mezzotint ⁴⁶
- H Pedhammok Sir William Osler, Bart (1849-1919) ⁴⁷
- I Potter, Caryl Sir William Osler—An Appreciation ⁴⁸
- J Thayer, W S William Osler ⁴⁴
- K Rawnsley, H D Sir William Osler In Memoriam ⁴⁹

37 Lighthall, W D Person of Evolution The Outer Consciousness, the Outer Knowledge, the Directive Power, Studies of Instinct as Contributions to a Philosophy of Evolution, New York, The Macmillan Company, 1930

38 Osborne, M The Song of Israfel and Other Poems, Toronto, The Macmillan Company, 1923

39 Riesman, D History of the Interurban Club, 1905-1937, Philadelphia, John C Winston Company, 1937

40 Thayer, W S Osler and Other Papers, Baltimore, Johns Hopkins Press, 1931

41 Emmons, E To Sir William Osler (Further bibliographical information not available)

42 Hoffman, F L Sir William Osler (in Memoriam), Pub Health J **3** 435-436, 1920

43 Nimeh, W The Mission of the Physician, in Alminar de la Medicina arabe, Mexico City, privately printed, 1944

44 In Abbott ⁹ p 429

45 In Song of Israfel and Other Poems ³⁸

46 Osborne, M William Osler A Mezzotint, Canad J Med & Surg **1** 43-46, 1921

47 Pedhammok Sir William Osler, Bart (1849-1919) Stanzas written in commemoration of the first anniversary of Sir William Osler's death, Baltimore, Industrial Printing Company, 1921

48 Potter, C Sir William Osler—An Appreciation, M Mentor **2** 247, 1931

49 Rawnsley, H D Sir William Osler In Memoriam, Oxford Mag **38** 182, 1920

The esteem in which Osler was held is revealed again in the number of people who paid homage by dedicating to him their own contributions to literature or science. In the *Bibliotheca Osleriana*,⁵⁰ references to twenty such books are given, the present list contains additional titles

MEDALS

A Sir William Osler Medal, Oxford University

B The William Osler Medal of the American Association of the History of Medicine

C Osler Medal, Vancouver Medical Association

A Oxford University

After Osler's death, friends from Canada, the United States and England decided to perpetuate his memory at Oxford, they created the gold medal quinquennial award for presentation to the Oxford graduate who has made the most valuable contribution in the science, art and literature of medicine, and who has not previously received the medal. On the obverse side is the replica of the F. Vernon head of Osler, on the reverse is inscribed "Willelmus Osler, Medicinae Professor Regius MCMIV-XIX." Recipients of the honor have been Sir Archibald Edward Garrod, D.M., Regius Professor of Medicine, Student of Christ Church (1925), Sir Wilmot Parker Herringham, D.M., Keble College (1930), Sir Arthur Frederick Hurst, D.M., Magdalen College (1935), Sir Edward Farquhar Buzzard, Bart., K.C.V.O., D.M., Regius Professor of Medicine, Student of Christ Church (1940), and Prof. Claude Gordon Douglas, B.Sc., D.M., Fellow of St. John's College (1945).

B American Association of the History of Medicine

In 1941, the American Association of the History of Medicine established the William Osler Medal, to be awarded annually to a medical student of the United States or Canada who submits the best essay in original research in the history of medicine, or whose essay best reflects an appreciation and understanding of a subject in medical history. The medal has been awarded to John T. Barrett, Boston University School of Medicine (1942)⁵¹, George Edward Murphy, University of Pennsylvania School of Medicine (1943)⁵², Willard L. Marmelszadt, Tulane University School of Medicine (1944)⁵³, Peter Kellaway, McGill University (1946)⁵⁴ and Honor M. Kidd, McGill University (1947)⁵⁵. No award was made in 1945 or in 1948.

50 Osler, W. *Bibliotheca Osleriana. A Catalogue of Books Illustrating the History of Medicine and Science*, Oxford, Clarendon Press, 1929.

51 Barrett, J. T. *The Inoculation Controversy in Puritan New England*, *Bull Hist Med* **12** 169-190, 1942.

52 Murphy, G. E. *The Evolution of Our Knowledge of Rheumatic Fever. An Historical Survey with Particular Emphasis on Rheumatic Heart Disease*, *Bull Hist Med* **14** 123-147, 1943.

53 Marmelszadt, W. L. *The Musical Sons of Aesculapius*, New York, Froben Press, Inc., 1946.

54 Kellaway, P. *The Part Played by Electric Fish in the Early History of Bioelectricity and Electrotherapy*, *Bull Hist Med* **20** 112-137, 1946.

55 Kidd, H. M. *Pioneer Doctor John Sebastian Helmcken*, *Bull Hist Med* **21** 419-461, 1947.

C Vancouver Medical Association

The medal is given to the speaker who delivers the Osler Lecture, previously described

PLAQUES, MEDALLIONS AND TABLETS

- A Bronze memorial plaque by F Vernon of Paris, unveiled in the court of the University Museum at Oxford, June 10, 1925⁵⁶
- B Memorial portrait medallion of Sir William Osler by R Tait McKenzie for Johns Hopkins, a gift of Osler's associates and assistants at Johns Hopkins
- C Memorial tablet in the main corridor of the Montreal General Hospital
- D Vernon plaque, Medical Library, Johns Hopkins Hospital
- E Replica of R Tait McKenzie medallion, McGill University Medical Library
- F Dedicatory plaque, Trinity College School, Port Hope, Ontario
- G Tablet, Trinity Church, Bond Head, Ontario
- H Tablet, William Osler Memorial Building, Philadelphia General Hospital
- I Tablet, Ewelme Church, Oxfordshire, England

A, B, C

The first three memorials are described in the Abbott memorial volume⁹ and are here indicated only for the sake of completeness

D Vernon Plaque

A replica of the plaque at Oxford has been placed in the library of the medical department of the Johns Hopkins Hospital, on the fifth floor of the dispensary building. A small reproduction is hung in the lobby of the Osler Medical Clinic of the hospital.

E Replica of R Tait McKenzie Medallion

Adorning a wall in the general medical library at the McGill University Medical School is a plaster reproduction of the original medallion in the Johns Hopkins Hospital.

F Dedicatory Plaque, Trinity College School

A tablet, placed in the science classroom building on the stairway leading to the laboratories, bears the inscription

The Science Laboratories
were given in memory of
William Osler
First Head Boy of the School
and of his only son
Revere
who was killed in the Great War

⁵⁶ Jacobs, H B Foreword, in Abbott³⁰

G Tablet, Trinity Church, Bond Head

On a wall adjoining the Osler memorial window, over a small altar, is an impressive tablet to Osler's memory. The inscription records the essential details of his life.

H Tablet, William Osler Memorial Building, Philadelphia General Hospital

The Osler Memorial Building, in the courtyard of the Philadelphia General Hospital, is marked with a bronze tablet adjoining the window of the autopsy room. It bears the inscription:

As a Memorial to
William Osler, M.D.

This old autopsy house
has been restored by
John Wyeth & Brother, Inc.
of Philadelphia

Dedicated June eight, MCMXL

"I, too, miss Old Blockley"

—William Osler, February 27, 1890

I Tablet, Ewelme Church

In the little village of Ewelme, 14 miles from Oxford, there is an almshouse for thirteen old men. It was endowed by Alice, Duchess of Suffolk, the granddaughter of Chaucer, the poet. Osler, as Regius Professor of Medicine, was Master of the Almshouse. No one holding this position before had done so much for the residents or was so beloved by them as he. In recognition of his association with the place, a tablet was erected on the death of Lady Osler.

In Memory of
SIR WILLIAM OSLER, Bart, F.R.S.
Born at Bond Head, Ontario
12th July, 1849
Died in Oxford
29th December, 1919

Regius Professor of Medicine, University of Oxford
Master of Ewelme Hospital, Professor of the Institutes
of Medicine, McGill University. Professor of
Clinical Medicine, University of Pennsylvania, and
Professor of Medicine at Johns Hopkins University

Also of his wife
DAME GRACE REVERE OSLER
Born in Boston, U.S.A.
19th June, 1854
Died in Oxford
31st August, 1928

And of their Son
EDWARD REVERE OSLER
2nd Lieut., R.A.
Born in Baltimore, U.S.A.
28th December, 1895
Died of Wounds in Flanders
30th August, 1917

MEMORIAL BUILDINGS AND MEDICAL UNITS

- A Bibliotheca Osleriana, McGill University
- B Osler Medical Clinic, Johns Hopkins Hospital
- C Osler Hall, Academy of Medicine, Toronto
- D Science laboratories, Trinity College School, Port Hope, Ontario
- E Osler Ward, Duke University, Durham, N C
- F Osler Memorial Building, Philadelphia General Hospital
- G Osler House, Oxford
- H Osler Sanatorium, Headington, Oxfordshire

A Bibliotheca Osleriana ⁵⁷

During Osler's lifetime he collected a remarkable library, illustrating the history of human thought, scientific and medical. Among the books are some of the rarest of all publications. The collection was bequeathed to his alma mater, McGill University, and reposes in a beautiful, especially constructed room in the medical building of the university. The priceless treasures have been completely detailed in the catalogue of the Bibliotheca Osleriana,⁵⁸ a stupendous intellectual achievement. Osler started it but was unable to finish the task. It was completed by W W Francis, Archibald Malloch and R H Hill, of the Bodleian Library. Dr Francis, the librarian who has cared for this collection, is the living authority on the life and writings of Osler. In an alcove behind a replica of the Vernon plaque, surrounded by his own publications and his precious collection of the books of Sir Thomas Browne, the ashes of Osler and his wife have been placed in a bronze casket. The dedication of the great library was a high tribute to him. The dignity of the ceremony was reflected in the address of the day by Dr William S Thayer,⁵⁹ Osler's former assistant. Every detail would have pleased the Chief, his presence was very real. Thayer's remarks were full of personal references to the immortal influence of Osler's greatness. Finally, he very cleverly expressed his own thoughts as though they were being spoken by the books themselves. While at Oxford, Osler, by virtue of his position as Regius Professor of Medicine, was made a curator of the Bodleian Library. In recognition of his services and to commemorate his association, the curators sent, as their representative to the dedication of the Bibliotheca Osleriana, R H Hill. He brought with him congratulatory greetings and, again, high praise, expressed in the broadside reproduced in the illustration.

B Osler Medical Clinic

In 1931, the board of trustees of the Johns Hopkins Hospital, in recognition of the fact that Osler was the first professor of medicine at the university and had established the great department of medicine, honored his memory by naming the new medical building the Osler Medical Clinic. At that time, Thomas C Corner,

⁵⁷ In Abbott⁹ Francis, W W. The Osler Library, Bull Johns Hopkins Hosp **46** 78-82, 1930, Osler's Shrine, Bull M Library A **26** 1-2, 1937.

⁵⁸ Osler⁵⁰ Garrison, F H. The Osler Catalogue, Bull New York Acad Med **5** 860-861, 1929.

⁵⁹ Thayer, W S. An Address on the Occasion of the Dedication of the Osler Library, Canad M A J **21** 1-4, 1929.

who had painted a life-size portrait of Osler in 1905, before his departure for England, presented the painting to the hospital. It has since hung in the lobby of the Osler Medical Clinic.

C Osler Hall

At a meeting of the Ontario Medical Library Association held in 1898, Osler suggested that the various medical societies of Toronto be amalgamated. Eventually, they did join and formed what is now the Academy of Medicine of Toronto. Osler was well known in Toronto, having attended Trinity College before going to Montreal, he had many associations with the medical life there. He was especially interested in the academy and contributed generously to the library with his own writings, bound journals and rare editions. He was instrumental in having his brother, Sir Edmund Osler, present to the academy fifty-eight rare medical engravings that he had selected, many of them are annotated in his own handwriting. The academy also possesses the only authorized replica of Osler from the Sargent painting of the four professors at Johns Hopkins. Therefore, it seemed natural that the members of the academy should in some way honor him, and they dedicated Osler Hall to him. Among the treasures are first editions, photographs and other articles of Osleriana. With the collection are various mementoes of the lives of Osler's beloved teachers, Father Johnson and Dr. James Bovell.

D Science Laboratories

As a boy, Osler attended Trinity College School at Weston, Ontario (it is now situated at Port Hope). Since his day, succeeding generations of the Osler clan have attended the school. It is a great pride to the headmaster and all connected with that institution that Osler was the first "head boy." The school was rebuilt from 1928 to 1930, after a fire, as a memorial, members of the Osler family gave the third floor of the new classroom building for the department of science, including large laboratories for chemistry and physics, in an adjoining workshop are facilities for developing and printing films, and a very large room used for art work. It is in this building that the dedicatory plaque is placed.

E Osler Ward

At Duke Hospital the names of fourteen eminent physicians and surgeons were chosen for the wards, the women's ward, of thirty beds, in the medical service is called the Osler Ward.

F Osler Memorial Building⁶⁰

When Dr. Kenneth M. Lynch, of the Medical School of South Carolina, was resident pathologist at the Philadelphia General Hospital, he was deeply impressed by the still-lingering tradition of Osler's years at that institution and felt that the "little old shrine of ambition and hard work," the old "Post House," should be created a memorial to Osler. The idea was greeted with unanimous enthusiasm, and in 1931 the name of the "Post House" was changed to Osler Memorial Building. The firm of John Wyeth & Brother, Inc., was responsible for the restoration and presented the Dean Cornwell painting. The dedication ceremony took place on June 8, 1940 in the auditorium of the administration building, opening with a premier exhibit of the Cornwell painting, which received much praise from those familiar with the early days. The first remarks were a tribute by Dr. William E. Robertson to Dr. David Riesman—for years consultant at the hospital.

⁶⁰ Hunter, R. J., and others. Dedication of the Osler Memorial Building of the Philadelphia General Hospital, "Old Blockley," June 8, 1940, *Bull. Hist. Med.* 10: 57-104, 1941.



THE CURATORS OF THE BODLEIAN LIBRARY at Oxford send their greetings to the Chancellor, the Vice-Chancellor, and the Governors of McGill University on the occasion of the Dedication of the Osler Library. They remember with gratitude the presence of Sir William Osler as their colleague, the keen interest which he at all times displayed in the welfare and development of the University Library at Oxford, and the inspiration which his words of counsel brought. They view with particular satisfaction this fulfilment of the pious intentions of Sir William Osler, so ably furthered by Lady Osler—the installation of the Osler Collection in his Alma Mater of McGill, and the completion and publication of the Bibliotheca Osleriana, and they are glad to send as their representative one who is privileged to be intimately associated with the culmination of both these aims. From the early home of experimental science, with full realization of the functions of the great university libraries in the preservation of the records of scientific progress, the Curators of the Bodleian Library send their cordial congratulations, and feel confident that the Osler Library will diffuse the spirit and advance the ideals of its Founder.

15 May 1929

Broadside brought by R. H. Hill to the dedication of the Bibliotheca Osleriana,
McGill University. Lent by E. Rosencrantz, M.D.



"Osler at Old Blockley," painted by Dean Cornwell, N.A. Lent by E. Rosencrantz, M.D.



Replica of the portrait of Sir William Osler painted in Paris during the winter of 1908-1909 by S Seymour Thomas and exhibited in the Paris Salon of 1909. The original is in the possession of the artist, at La Crescenta, Calif., the reproduction, shown here, will eventually be given to the University of California Medical School by E. Rosencrantz, M.D., who lent this photograph



Memorial stained glass window in Trinity Church, Bond Head, Ontario, adapted from Hoffman's painting, "Christ Healing the Sick" Photograph lent by E Rosencrantz, M D



Fanciful painting of Osler and "little Janet" by E L Chase Photograph lent
by E Rosencrantz, MD



Dundas cairn, monument to Sir William Osler in Dundas, Ontario Photograph
lent by E Rosencrantz, M D

and active on the committee for the celebration—who had recently died Dr William E Hughes, a former student, gave a few reminiscences, and Dr Joseph McFarland related anecdotes The outstanding address of the afternoon was given by Dr W G MacCallum, a student of Osler's at Johns Hopkins and a fellow countryman, and at that time professor of pathology at the Philadelphia General Hospital He briefly listed the essential factors that shaped Osler's career his home influence, student days here and abroad, original investigations and contributions to medicine, and his friendship with the great medical men Dr MacCallum stressed Osler's clinical knowledge, almost invariably proved by pathologic findings After the exercises, the old "Post House" was opened to visitors On display were the record books with the autopsy findings in Osler's own handwriting, and on the wall was the colorful Cornwell painting In the autopsy room are the table, desk and cabinet used by Osler The museum occupying the two upper rooms contains photographs, writings and other memorabilia about this rare soul

G Osler House

The Observer's House at Oxford, now used as the administration building for the Nuffield Trust, has had the name changed to the Osler House at the request of Lord Nuffield

H Osler Sanatorium

The tuberculosis sanatorium at Headington, Oxfordshire, in deference to Osler, is called the Osler Sanatorium

CLUBS AND SOCIETIES

A Osler Historical Club, Medical and Chirurgical Faculty of Maryland

B Osler Club of London

C Osler Society of the McGill University Faculty of Medicine

D Osler Reporting Society, Royal Victoria Hospital, Montreal

E Osler Club of New York

F The Osler Club, Trudeau Sanatorium, Trudeau, N Y

G Osler Clinical Society of the University of Vermont

H The Osler Society of Oxford

I Osler Society, University of Western Ontario

J William Osler Society, Tufts College Medical School

K Osler Society of Alberta

A Osler Historical Club

In January 1896, in order to raise money for the library of the Medical and Chirurgical Faculty of Maryland, a book and journal club was organized at Osler's home, with Osler as president By the following year the programs were entirely devoted to papers on the history of medicine After twenty-five years the subscriptions were discontinued, and the club became a part of the Medical and Chirurgical Faculty In 1929, the name was changed to the Osler Historical Club, after its founder "because of his inspiration it has continued to live these thirty-two years"

B Osler Club of London

The Osler Club of London was formed in April 1928 by a group of students for the study of the history of medicine and its relation to our times. In acknowledgment of the inspiration of the life and works of Osler, the club was named after him. The original members were six in number. The meetings have always been characterized by an atmosphere of informality which it is thought would have pleased Osler. The club has grown quietly throughout the years, members have brought interested friends to meetings, and they in turn have become members. The only qualification necessary is an interest in medical history, among the members today are medical students, physicians, librarians of many of the famous London medical libraries and men of letters. There were no meetings during the war, after the cessation of hostilities a notice was inserted in the medical journals and hospital magazines announcing the resumption of meetings and requesting the names of those interested. There are now seventy-seven members, including three of the founders. There have been seventy-nine meetings (to January 1949), which have been addressed by guest speakers as well as by members of the club, the papers have concerned various topics pertaining to medical history. Every year, when the club has been active, there has been a celebration of Osler's birthday on July 12, with either a dinner or a special meeting. The programs have consisted of orations or symposiums of commemoration. The guest speakers and their subjects have been

1928 Sir Wilmot Herringham	Oration
Sir Humphry Rolleston	Osler Eulogy
1929 Sir Archibald Garrod	"The Power of Personality"
1930 Harvey Cushing	Informal dissertation
1931 William Stobie	Osler and Tuberculosis"
(Mayor of Oxford)	
1932 R. W. Chapman	"Book Production in the Eighteenth Century"
1933 Langdon Brown	"The Psychology of Authorship"
1934 John Beattie	"The Osler Apocrypha"
1935 John F. Fulton	"Frascatorius"
1936 Lord Horden	"Septic Endocarditis"
1937 A. G. Gibson	"Thomas Willis, Practitioner and Scientist"
1938 Meeting held, no record	
1947 John F. Fulton	"Medical Biography"
1948 Symposium	
William Stobie	"Osler as a Physician"
Sir Arthur MacNalty	"Osler as a Scientist"
Unknown	Osler the Bibliographer"
W. R. Bett	"The Osler Legend"
A. W. Franklin	"The History of the Osler Club"

C Osler Society, McGill University Faculty of Medicine

The Osler Society of the McGill medical school consists of thirty to forty undergraduates interested in Osler and the history and literature of medicine. The members are chosen by fellow undergraduates, mostly from the second year students. The society meets once a month in the beautiful Bibliotheca Osleriana, at the gatherings, two or three papers are read by members of the senior class. The annual banquet is the affair of the year and is attended by graduates and members of the faculty. A distinguished physician is invited to deliver an address, and a large silver cigar box and decanter which belonged to Osler are passed among the group.

D Osler Reporting Society, Royal Victoria Hospital

At the Royal Victoria Hospital in Montreal, a group of young clinicians formed an Osler Reporting Society about 1920. The society meets once a month during the winter for informal discussion of clinical subjects.

E Osler Club of New York

In 1935, a group of graduates of Johns Hopkins Medical School, to promote fellowship, to help recent graduates and to enjoy together their broad cultural

interests, formed the Osler Club of New York. Membership of the group was limited to thirty graduates of less than twenty-five years, an unlimited number of those of more than twenty-five years and five honorary members, selected from outstanding graduates in any locality. The group held four meetings a year until the outbreak of the war, when activities were temporarily suspended, plans are progressing for reorganization. Dr. Norman B. Gwyn presented the club with its gavel, made from the wood of a window frame in the house where Osler was born.

F The Osler Club, Trudeau Sanatorium

The Osler Club was started about 1929 by Dr. Lawrason Brown. The object is to meet two or three times during the winter months and to present papers pertaining to the historical aspects of medicine. The members and speakers are chosen from the physicians who practice in Saranac Lake or who are on the staffs of the various sanatoriums in that region.

G Osler Clinical Society, University of Vermont

The Osler Clinical Society of the medical school of the University of Vermont was organized in 1929 for the purpose of bringing outstanding medical men to address the society at regular meetings. At the beginning of the school year there is a general meeting for the election of officers and for the appointment of a committee to aid in the selection of speakers. At the end of the school year the society sponsors a dinner dance to bring all the students together socially. Usually there are about five speakers each year.

H The Osler Society of Oxford

The Osler Society of Oxford is made up of undergraduates and holds meetings every month in the different colleges. During the war there were no meetings, but recently they have been resumed.

I Osler Society, University of Western Ontario

Membership in the society is open to all undergraduates who display an interest in the society by attending three of the four meetings during the year. Discussions are opened by a faculty member, and a student gives a paper relating to medical history. The honorary president, chosen once a year, delivers an address at the annual banquet.

J William Osler Society, Tufts College Medical School

Under the influence and guidance of Dr. Joseph Pratt, the society was established at Tufts many years ago as an honor society. In 1940 it was merged with Alpha Omega Alpha, when the beta chapter of that fraternity was formed at Tufts.

K Osler Society of Alberta

The society devotes a part of its activities to medical history.

COLLECTIONS

A Welch Medical Library, Johns Hopkins Medical School

B Yale Historical Library

C Duke University School of Medicine

D Boston Medical Library

E William Bradley Collection, College of Physicians, Philadelphia

F University of California Medical School

A Welch Medical Library

The library at Johns Hopkins School of Medicine is rich indeed in mementoes of Osler. On the deaths of his former confrères, Drs Halsted, Welch, Kelly, Thayer and others, their Osleriana were presented to the library. Because of limited help during the war, it was not possible to undertake the task of cataloguing the enormous amount of material, however, complete organization is planned, and this undoubtedly will stand as one of the great Osler collections.

B Yale Historical Library

To Yale belong some of the choicest of Osler items. Here are housed all of Harvey Cushing's enormous accumulation of papers and his intimate correspondence with the Oslers throughout the many years of their close friendship. The historical data relative to every phase of Osler's life are unique in content, for they reflect intimately the personal aspect of events Oslerian.

C Duke University School of Medicine

Dr Wilburt Davison, dean of the Duke University School of Medicine, has gathered a large number of Osler writings and memorabilia, which have formed the nucleus of the collection at that institution.

D Boston Medical Library

Here are assembled, in chronologic order, all the editions, printings and translations of Osler's great textbook of medicine. One finds on the shelves the scarce English "pirate" edition (from the American fourth edition, 1901), and the rare Chinese first edition in parts. The fine collection was made by Dr Henry R. Viets, a devoted admirer of Osler, and was presented by him to the library.

E William Bradley Collection

Dr William Bradley of Philadelphia presented a collection of photographs of much interest, pertaining to physicians and to medical events and places of interest in and about the city of Philadelphia. An important part of the collection is the series of forty-two photographs, illustrating data both about Osler concerning his lifetime and the tributes since his death. The prints, uniform in size, represent various phases of his life and include his personal photographs and reproductions of oil paintings, busts, poems, letters, tablets and plaques. An index describes in detail the artist or author, date, source and location of the original.

F University of California Medical School

In the historical section of the University of California Medical Library there has been assembled a large collection of Osler material. It represents nearly all the writings about him. In addition, there are numerous memorabilia, holographic manuscripts and letters, family papers and photographs and two original oil paintings, made by S. Seymour Thomas. Among the cherished possessions are autographed reprints and journals used by Cushing in writing the "Life", many are inscribed with comments and notes made by him, and passages have been marked. Since Cushing possessed duplicates, he gave these to a favorite student, Dr Mayo Soley, who generously passed them on to me. The collection is of special interest because it has been fully annotated and catalogued, so as to be of use to future scholars and students. It is planned to give a detailed account of the treasures sometime in the near future.

MISCELLANEOUS TRIBUTES

A William Grant Stewart Memorial

B Bookplates

C Oil paintings

D Memorial window

E Dundas cairn

F Osler Day

G Osler scholarship

H Pullman car •

A The William Grant Stewart Memorial

Under the provisions of the will of Dr William Grant Stewart, a practicing physician of Montreal, a copy of Osler's "A Way of Life" is given to each medical student at McGill University on his entering the second year. The well known address was presented to Yale students in April 1913. A year before his death, in 1927, Dr Stewart personally made the first presentation. On the inside cover of each copy is printed a charming bookplate, with a sketch of Osler's head and the inscription

"Presented to

'To have striven, to have made an effort,
to have been true to certain ideals—
this alone is worth the struggle'
(From Osler's *An Alabama Student*)"⁶¹

In making the bequest, Dr Stewart wrote "I consider this a beautiful lay sermon. I am giving it with the hope that seed will fall into good soil and bring forth some one hundred fold, some sixty, some thirty."

B Bookplates

In November 1919, shortly before the death of Osler, Max Brodel made a characteristic bookplate for the books purchased from the Osler Fund of the Library of the Medical and Chirurgical Faculty of Maryland. While Dr Fielding H. Garrison was librarian at the Welch Medical Library, he built up a collection of important works on the history of medicine for presentation to the library as an Osler collection. As a bookplate he used his own, somewhat modified. Because of his untimely death, the list of books is not extensive.

C Oil Paintings

"Osler at Old Blockley." The firm of John Wyeth & Brother, Inc., arranged with Dean Cornwell, the artist, for a series of paintings portraying notable figures in American medicine. "Osler at Old Blockley" was the second of the series. The painting was unveiled at a dinner given by the president of the company at the Penn Athletic Club in November 1939, the guests were members of the committee for the Osler Memorial Building. The original painting is available to medical groups as a loan and is continually on exhibit in various parts of the United States. In the museum of the Osler Memorial Building at the Philadelphia

⁶¹ Osler, W. *An Alabama Student, and Other Biographical Essays*, New York, Oxford University Press, 1908.

General Hospital, a full-sized reproduction is on display, eventually, the original painting will be placed there permanently

The pharmaceutical house of Parke, Davis and Company, in 1930, commissioned E L Chase to make an oil painting. It has no real title, but bears the inscription "To the world—a great physician, to the child—a beloved goblin". The original painting, which measures about 19 by 27 inches, is a fanciful picture of Osler and "little Janet", it was made from the touching description in the Cushing biography of Osler⁶². The painting is used by the firm as an advertisement and has been reproduced in several publications⁶³.

D Memorial Window

In Trinity Church at Bond Head is the beautiful stained glass memorial window dedicated to Sir William Osler. The window is an adaptation of Hoffman's painting of Christ healing the sick. It was presented by the Simcoe County Medical Association.

E Dundas Cairn

The monument erected by the Hamilton Medical Society to perpetuate the memory of Osler in that vicinity stands on a little hill at the eastern entrance to the town of Dundas, Ontario, about 100 feet from Osler's old home, the Rectory. The location was chosen because it overlooks the marsh from which Osler obtained the specimens that interested him in biologic studies as a boy. The cairn is composed of granite rocks of that region. The dedication took place on Dec 29, 1927, amidst a large gathering of friends and physicians and other inhabitants of the community. Dr Norman Gwyn of Toronto, Osler's nephew, unveiled the cairn. On the face of the cairn is a beautiful bronze tablet, bearing an inscription in relief:

Erected by the
HAMILTON MEDICAL SOCIETY
To Commemorate the Life of
SIR WILLIAM OSLER, BART
Student, Philosopher, and Physician
whose early studies of nature in this
vicinity laid the foundation of his career
He said "The Master Word is Work"
October, 1927

F Osler Day

This special celebration was first held on Dec 27, 1935 at Hamilton⁶⁴. The date was chosen to commemorate the publication, in February 1869, of Osler's first paper, "Christmas and the Microscope"⁶⁵. The custom was inaugurated by the Hamilton Academy of Medicine, in cooperation with the City Hospitals, the Hamilton Health Association, McMaster University and the Osler Memorial Committee of the Canadian Medical Association. During the morning hours, clinics were held at the general hospital, and in the afternoon, the Mountain Sanatorium was visited, then a pilgrimage was made to Dundas to see the cairn, the marsh, the Rectory,

⁶² Cushing,¹ p 620

⁶³ *Sat Eve Post* 203 55, 1930, *Child Life* 10 399 (Aug) 1931

⁶⁴ An Osler Day, editorial, *Canad M A J* 32 427, 468, 1935

⁶⁵ Osler, W. Christmas and the Microscope, *Hardwicke's Science-Gossip* 5 44, 1869

where Osler had lived as a boy, and the office where he first saw patients as locum tenens. On the return to Hamilton, a reception was given at McMaster University. At a meeting of the Hamilton Academy of Medicine, Dr. Thomas B. Fletcher gave the after-luncheon address.⁶⁶

G Osler Scholarship, Canadian Medical Association²⁵

At the inauguration of the Osler Memorial Oration, it was announced that J. W. McConnell had contributed \$6,000 to the Canadian Medical Association as a nucleus for a trust fund for an Osler Scholarship. A similar amount had been given by the president and five members of the board of the Montreal General Hospital, in recognition of Osler's association with that institution. It is planned that the interest from the fund shall be available each three years for a candidate to undertake special work that will fit him better for teaching clinical medicine.

H Pullman Car

Among the unusual tributes is the Pullman car "William Osler," regularly operating as a part of the train known as the "West Coast," on the Los Angeles to Portland service of the Southern Pacific Railroad.

These tributes—almost countless, varied, impressive—come from groups of friends with memories, from an unbelievable number of persons who benefited from their contact with Osler, from medical societies, from distinguished physicians in Canada, the United States and England, from his colleagues and students who were inspired, guided and helped by him. They desired to show their respect for him and to perpetuate his influence by these tributes.

⁶⁶ Fletcher, T. B. Address on the Importance of Bed-Side Study and Teaching, *Canad. M. A. J.* 32: 357-364, 1935.



—Courtesy Dr Loyal Davis

"The front door at the back" of "The Open Arms," 13 Norham Gardens,
Oxford

GASTROSCOPIC AND HISTOLOGIC APPEARANCE OF THE GASTRIC MUCOSA BEFORE AND AFTER VAGOTOMY FOR PEPTIC ULCER

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LESTER R DRAGSTEDT, M D

AND

WALTER LINCOLN PALMER, M D

CHICAGO

THE PURPOSE of this paper is to describe the appearance of the gastric mucosa before and after vagotomy. A total of 125 gastroscopies were performed on 27 patients, 26 of whom had peptic ulcer and 1 of whom had a functional gastrointestinal disturbance, 18 were examined before and after operation and 9 after vagotomy only. The criteria for the diagnosis of gastritis were essentially those formulated by Schindler¹. The stomach also was examined histologically in 11 patients, in 3 at the time of resection of a gastric ulcer, developing approximately five months to four years after vagotomy, and in 8 at autopsy, performed from one week to two years and three months after operation.

Wolff² examined gastroscopically 8 patients with duodenal ulcer and 3 with gastric ulcer, one week to eleven months after vagotomy, and observed a dull and reddened mucosa in 7 and a normal mucosa in 4. Gastric tonus was diminished, retention of food, blunting of the angulus and obliteration of the musculosphincter of the antrum were noted. The last two changes disappeared temporarily in the 3 patients given urecholine® (carbaminoyl-beta-methylcholine chloride) subcutaneously. The gastric ulcers healed promptly. Wolf and Andrus³ noted pallor of the mucosa after vagotomy in a patient with gastrostomy. Spontaneous motor activity was absent, but mild hyperemia and engorgement were

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1 Schindler, R. Gastritis, New York, Grune & Stratton, Inc., 1947.

2 Wolff, R. The Gastroscopic Appearance of the Gastric Mucosa Before and After Vagotomy, *Gastroenterology* **10** 231, 1948.

3 Wolf, S, and Andrus, W D. The Effect of Vagotomy on Gastric Function, *Gastroenterology* **8**:429, 1947.

observed after the ingestion of a meal, the injection of neostigmine methylsulfate U S P produced hyperemia, though it was less pronounced than before vagotomy

Paulson and Gladsden⁴ observed no alterations in the appearance of the gastric mucosa in patients with vagotomy alone, however, peristaltic activity was decreased. In persons with vagotomy and gastroenterostomy "some negligible mucosal changes" were sometimes present. In patients with vagotomy and partial gastric resection, the edema, thickening and nodular hypertrophy, with or without erythema and friability, were regarded as similar to those changes noted in the absence of vagotomy

Asher⁵ performed gastroscopy in 20 cases, 19 of duodenal ulcer and 1 of a jejunal ulcer, at intervals of from three to twelve months after vagotomy alone or combined with pyloroplasty or gastroenterostomy. Of the 8 cases in which vagotomy alone was done, preoperative examination was made in 4, superficial changes were noted in 2, hypertrophic changes in 1 and a normal mucosa in 1. A postoperative diagnosis of superficial or hypertrophic gastritis, with or without erosions, was made in 6 cases, of erosions alone in 1 case and of a normal mucosa in 1 case. Normal motility was recorded in 5 cases of this group, spasm and atony were noted in 1 case each, and atony and spasm in 1 case, on separate examinations. Of the 12 cases in which vagotomy and gastroenterostomy or pyloroplasty was performed, a preoperative examination had been made in 7, a diagnosis of normal mucosa had been made in 2, of superficial gastritis in 4 and of a severe, mixed type of stomal gastritis in 1. After operation, superficial or hypertrophic inflammation with or without erosions, was noted in 7 cases, atrophy in 1 and a normal mucosa in 3, an erosion was observed in 1 case three months after vagotomy but the mucosa appeared normal three months later. Normal motility was seen in 1 case, spasm in 5, decreased motility in 1 and atony in 4, in 1 case spasm was noted three months after vagotomy, but motility appeared normal gastroscopically three months later.

GASTROSCOPIC OBSERVATIONS BEFORE AND AFTER VAGOTOMY

Duodenal Ulcer—The data on the 14 patients with duodenal ulcer and the 3 patients with both duodenal and gastric ulcer are summarized in table 1. Gastric retention was present in 5 of the 6 patients treated with vagotomy alone, the retention was temporary in the 2 patients of this group who were examined more than once. Retention was not

⁴ Paulson, M., and Gladsden, E. S. Medical Aspects of Vagotomy for Peptic Ulcer, *Bull. Johns Hopkins Hosp.* **81**: 107, 1947.

⁵ Asher, L. M. The Gastric Mucosa After Vagotomy for Peptic Ulcer. A Gastroscopic Study. *Gastroenterology* **11**: 303, 1948.

observed gastroscopically in 10 of the 11 patients in whom a gastroenterostomy had been established prior to, or concomitantly with, the vagotomy. The appearance of the mucosa had not changed significantly in 9 of the 11 patients examined before and after operation, 5 originally presented a normal mucosa and 4 gastritis. The stomach appeared essentially normal after vagotomy in 2 patients for whom a diagnosis of moderate hypertrophic gastritis and superficial inflammation, respectively, had been made before operation. Gastroscopy was not performed before operation on 6 patients (cases 10, 11, 12, 13, 14 and 17), 3 of these presented a normal mucosa two, five and one-half and thirty months, respectively, after vagotomy. A moderate superficial gastritis was observed in 1 patient twelve months after vagotomy and gastroenterostomy. Superficial changes and a normal mucosa were observed at various examinations in another patient, during a postoperative period of twenty-six months. The superficial gastritis in the sixth patient, which appeared three years after vagotomy, may possibly have been related to the previously administered irradiation of the stomach. Rapid healing was observed in 2 of the 3 patients with concomitant gastric ulcer.

The insulin test for the integrity of vagal innervation, performed after operation on 12 patients, yielded negative results, a positive acid response was elicited in 1 patient (case 3) several months later. (The reliability of the insulin test as an indicator of complete or incomplete vagotomy has not been fully evaluated.) Gastric ulcers developed after vagotomy in 2 patients (cases 4 and 13), these cases, therefore, are described in more detail.

CASE 4—W. B., a 63 year old man with a duodenal ulcer of eight years' duration, had received a total of 1,260 r (depth dose) in divided amounts to the fundus and body of the stomach, for the purpose of reducing gastric acidity. The maximum free hydrochloric acid (histamine test) decreased temporarily from a range of 108 to 116 clinical units to 60, but returned subsequently to original levels, in the ensuing four years the amount of acidity fluctuated between 108 and 126 clinical units. Three gastroscopies during this period demonstrated, at various times, minimal superficial inflammation, pigmented areas and mild, localized, hypertrophic gastritis. The mucosa, fourteen months after trans-thoracic vagotomy, appeared normal, shallow peristaltic waves were observed in the antrum. Ulcer distress recurred four years and three months after operation, roentgenoscopy then disclosed a huge ulcer crater on the lesser curvature of the stomach. Gastroscopy demonstrated a large, benign ulcer on the anterior wall of the lesser curvature of the stomach, immediately above the angulus. The mucosa adjacent to the ulcer was reddened, edematous and hemorrhagic, but elsewhere it appeared normal. Peristaltic activity was vigorous. Free acid was present in the gastric content, the exact amount was not recorded. The result of the insulin test was negative. At operation, an intact vagus fiber was identified within the muscle layer on the posterior wall of the esophagus, and severed, a partial gastric resection was performed, with the removal of a benign ulcer. The microscopic appearance of the stomach is described later in this paper.

Case	Sex and Age	Before Vagotomy			After Vagotomy			Gastroscopic Observations	
		No of Examinations	Interval Before Operation	Gastric Mucosa	Type of Vagotomy	No of Examinations	Interval	Gastric Mucosa	Peristalsis
1 S R	M 18	1	1 days	Normal	Thoracic	1	3½ mo	Normal	Shallow +
2 R P	M 58	1	7 days	Essentially normal	Abdominal	1	3 mo	Normal	Moderate +
3 M	M 1	1	2 days	Moderate, superficial gastritis of the antrum	Abdominal	1	4 mo	Normal	Moderate Slight
4 L H	M 42	3	1 yr	Mild, superficial gastritis, hemorrhages, localized, hypertrophic gastritis	Thoracic	2	1½ mo	Normal	Shallow +
5 W B	M 63					2	4½ yr	Gastric ulcer above angulus, adjacent mucosa, edematous and hemorrhagic, elsewhere, normal	Active -
6 N R	M 45	1	2½ mo	Moderate hypertrophic gastritis	Abdominal	1	6 wk	Gastric mucosa normal, by perennia and edema at stoma	Present -
7 A V	M 48	1	7 days	Normal	Abdominal	1	9 mo	Normal	Present -
8 M L	F 50	2	3 yr, 8 mo 3 days	Mild, localized, superficial gastritis Normal, mild edema at stoma	Abdominal	1	4 mo	Normal	Present -
9 D O N	M 65	1	2 days	Moderate, hemorrhagic hypertrophic gastritis	Abdominal	1	3 mo	Mild hypertrophic gastritis, prominent rugae	Active -
10 O L	M 10	1	3 days	Moderate hemorrhagic gastritis, adherent mucus, prominent rugae	Abdominal	1	3½ mo	Mild hypertrophic and superficial gastritis	Active -
11 N W	M 51	0		Patients with Duodenal Ulcer, no Control Gastroscopy, Vagotomy, Alone or with Gastroenterostomy	Thoracic	9	5 mo 7 mo	Moderate, superficial gastritis Moderate, superficial gastritis, lesser curvature	Slight +
12 R K	F 44	0			Thoracic, later gastro enterostomy	1	8 mo 12 mo 14 mo 16 mo 18 mo 26 mo 2½ yr	Normal Mild, superficial gastritis Mild, superficial gastritis Normal Moderate, superficial gastritis Mild, localized, superficial gastritis Normal	Moderate Peristalsis was active at the third examination and remained active
13 W R	M 32	0			Abdominal and gastro enterostomy	1	12 mo	Moderate, superficial gastritis, hyperemic mucosa	Active -
14 M D	M 35	0			Abdominal	1	5½ mo	Essentially normal, gastric ulcer in lesser curvature, midportion of stomach	Active -
15 T D	M 40	1	2 days	Benign ulcer, lesser curvature, above angulus, mucosa normal	Thoracic, later gastro enterostomy	3	2 yr, 8 mo 2 yr, 10 mo 3 yr	Moderate, superficial gastritis Moderate, superficial gastritis, upper two thirds of stomach Moderate, superficial gastritis, upper two thirds of stomach	Active throughout -
16 R P	M 39	2	7 days 5 days	Mixed gastritis, mild, 2 small ulcers in midportion, body of stomach	Patients with Duodenal and Gastric Ulcers	1	14 days	Normal, gastric ulcer almost healed	Active -
17 J O	M 31	0			Abdominal and gastro enterostomy	1	4 wk	Mild hypertrophic and superficial gastritis, ulcers healed	Absent Slight
					Abdominal	1	2 mo	Small (8 x 4 mm) ulcer at angulus normal mucosa (ulcer smaller at roentgenoscopic examination than at original examination)	Active -

CASE 13—W R, a 32 year old man, underwent a transabdominal vagotomy, after having experienced ulcer distress for eight years. Symptoms recurred several months after operation, increased in intensity and, five months after operation, culminated in the passage of several tarry stools. The result of the insulin test was negative, the output of acid in the nocturnal gastric secretion was reduced. Gastrosocopy demonstrated a benign ulcer, approximately 2 to 3 cm in diameter, on the anterior wall of the lesser curvature, in the midportion of the stomach. The mucosa appeared essentially normal, peristalsis was noted in the antrum. A partial gastric resection was performed, with the removal of a benign ulcer. The microscopic appearance of the stomach is described later in this report.

Gastric Ulcer—The observations in the 9 cases of benign gastric ulcer are presented in individual case reports and are also summarized briefly in table 2.

CASE 18—In G C, a man of 67, gastroscopy one week before transabdominal vagotomy had demonstrated a benign ulcer on the anterior wall of the lesser curvature of the stomach and moderate superficial and atrophic gastritis. Partial healing of the ulcer was noted one month after operation, the mucosa appeared normal, despite gastric retention. The ulcer was not visible five months after operation. The mucosa in some areas appeared normal, while in other regions it was covered with mucus. Gastric retention persisted, although peristaltic activity was observed in the antrum.

CASE 19—A P, a man of 45, had received a total of 1,635 r (depth dose) in divided amounts to the fundus and body of the stomach three years before operation for the purpose of reducing gastric secretion. Six gastroscopies during this period disclosed a benign ulcer on the lesser curvature above the angulus, and, at different examinations, mild to moderate superficial gastritis, slight atrophy and (on one occasion) a normal mucosa. The ulcer, present three weeks before transthoracic vagotomy, had healed completely one month after operation. The mucosa appeared irregularly reddened. Peristalsis was absent, and gastric retention was pronounced.

CASE 20—H A, a man of 43, received a total of 1,160 r (depth dose), applied in divided amounts to the stomach approximately four years before transthoracic vagotomy, a second course of irradiation, comprising 1,600 r, was administered one month after operation. Fourteen gastroscopies performed during the pre-operative period demonstrated the healing and recurrence of a benign ulcer on the lesser curvature of the stomach, at the angulus. The mucosa initially appeared normal. Approximately two and one-half years before vagotomy, an hourglass deformity had developed in the midportion of the stomach, subsequently, atrophy was observed in the lower segment and superficial inflammation in the upper pouch. Severe hypertrophic and superficial changes were noted approximately one year before operation. Three gastroscopies were performed after vagotomy. Peristalsis was diminished or absent, gastric retention was pronounced. The hourglass deformity persisted, only the upper segment was visualized. Four months after vagotomy the mucosa in some areas appeared entirely normal. In other areas it was dull, reddened and hemorrhagic, there was a questionable superficial erosion on the lesser curvature near the cardia. At seven months the mucosa presented a dull, thickened appearance. At nine months dulness and hyperemia were noted in some regions and a normal mucosa

After Vagotomy

Case	Sex and Age	Before Vagotomy			Type of Vagotomy	No of Examinations	Post operative Interval	Gastric Mucosa	Gastroscopic Observations		
		No of Examinations	Interval Before Operation	Gastric Mucosa					Ulcer	Peristalsis	Reaction
18 G O	M 67	1	7 days	Ulcer, moderate, superficial and atrophic gastritis	Abdominal	2	1 mo 5 mo	Normal Moderate, superficial gastritis	Smaller Healed	Shallow Active	+
19 A P	M 45	6	2½ yr	Ulcer, mild to moderate, superficial gastritis, atrophic changes, normal mucosa (once)	Abdominal	1	1 mo	Mild, superficial gastritis	Healed	Absent	+
20 H A	M 43	11	1½ yr to 2 wk	Ulcer, initially, normal mucosa, later, hourglass contraction, superficial and atrophic changes, severe superficial and hypertrophic gastritis	Abdominal	3	1 mo	Hourglass contraction, normal areas, mucosa in areas dull, reddened and bled easily	Superficial	Shallow	+
21 G K	M 39	6	1½ yr to 2½ yr	Ulcer, severe, superficial gastritis, severe, hemorrhagic, erosive hypertrophic gastritis	Abdominal	5	2 mo 6 mo	Moderate, superficial and hypertrophic gastritis	Healed	Shallow	+
22 J A	M 46	11	2 yr 3 mo to 2 wk	Ulcer, varying degrees of hypertrophic gastritis, often severe, hemorrhages erosions	Thoracic	9	3½ mo 5½ mo 8½ mo 11 mo 13 mo 16 mo 22 mo 23 mo 4 yr, 8 mo	Moderate, superficial gastritis Hemorrhages, superficial gastritis Moderate, superficial gastritis Severe, superficial gastritis Mild, superficial gastritis Superficial, erosive gastritis	Healed	Shallow	+
23 J W	M 70	10	25 mo to 2 wk	Ulcer mild, superficial gastritis hemorrhages, moderate hypertrophic gastritis 2 wk before operation	Thoracic	2	2 wk 2 yr, 10 mo	Mild, superficial gastritis Large amount of mucus, mucosa essentially normal	Healed	Active	Slight Slight
24 A P	M 37	6	Gastroenterostomy 8 yr before vagotomy 6½ yr to 1 wk	Mild to moderate hypertrophic gastritis, hemorrhages, later, mild atrophy	Abdominal and gastro enterostomy	1	21 mo	Normal	Healed	Active	+
25 A N	F 66	0	Intragastric ulcer with gastric retention		Abdominal, local excision of ulcer	1	3 mo	Hourglass deformity, mucosa of upper segment normal	Healed	Active	+
26 I T	F 43	0			Abdominal	1	15 mo	Moderate atrophy mid portion rugae normal	Recurrence	Active	-

in other areas of the upper pouch. There was no evidence of ulcer. The acid response to histamine was approximately the same as before vagotomy.

CASE 21—G K, a man of 39, with diabetes mellitus, gastroscopy (on six occasions) before transthoracic vagotomy had demonstrated a very large, presumably benign ulcer on the posterior wall of the midportion of the stomach, severe gastritis was present, characterized by diffuse hyperemia, swollen—almost polypoid—folds and excessive amounts of mucus, pronounced hypertrophic, hemorrhagic, erosive gastritis was observed on one occasion. An interval of two and one-fourth years elapsed between the final control gastroscopy and vagotomy. Five examinations, performed during a postoperative period extending from two months to more than three years, demonstrated mixed hypertrophic and superficial gastritis, shallow peristalsis and retention of food and mucoid material. These changes persisted until three years and two months after vagotomy. Gastroscopy now disclosed a contraction of the midportion of the stomach, taking the form of a large fold extending from the anterior to the posterior wall. The fold was surmounted by a large, dark gray ulcer, approximately 1.5 cm in diameter, whose border was slightly irregular in contour, but sharply demarcated. The mucosa in some areas appeared normal, in others, dull and reddened, and elsewhere edematous with adherent mucus. The maximum free acidity after histamine stimulation was similar to that noted before operation.

CASE 22—J A, a man of 46, had had a total of 1,325 r (depth dose) applied in divided amounts to the fundus and body of the stomach approximately two years before operation. The maximum free acid (histamine test) three months later had decreased from 110 to 20 clinical units, but the quantity soon returned to its original level. Thirteen gastroscopies demonstrated the healing and recurrence of a benign ulcer on the lesser curvature, above the angulus. Severe hemorrhagic, hypertrophic gastritis was noted on seven occasions, and erosions were seen twice. Nine gastroscopies, performed during a period of three and one-half months to four and three-fourths years after transthoracic vagotomy, disclosed a variable, but occasionally severe, superficial gastritis. Approximately eight months after operation a shallow ulceration was noted at the angulus. Gastroscopy four years and eight months after operation demonstrated vigorous peristalsis, a grayish mucosa with hemorrhages and adherent mucus, and a small erosion in the area of the ulcer, above the angulus. Free hydrochloric acid was present in the gastric contents after histamine stimulation.

CASE 23—J W, a 70 year old man, with a recurrent ulcer of twenty-five years' duration, had undergone two operations elsewhere (local excision of the ulcer and, later, gastroenterostomy). Two courses of roentgen irradiation were applied to the fundus and body of the stomach. The first, of 1,500 r (depth dose), produced transient anacidity, with temporary healing of the ulcer, the second, given eighteen months later with a total dose of 1,671 r, had no demonstrable effect on gastric acidity. Ten gastroscopies revealed, during a period of two years, the healing and recurrence of a large gastric ulcer above the gastroenterostomy stoma, superficial gastritis and mucosal hemorrhages, a moderately severe, hemorrhagic, hypertrophic gastritis was present two weeks before transthoracic vagotomy. Two gastroscopies were performed subsequently. The examination two weeks after operation demonstrated healing of the ulcer, mild superficial gastritis and slight gastric retention. Two years and ten months later the mucosa appeared normal, despite persistent gastric retention, the ulcer had not recurred.

CASE 24—A F, a man aged 37, had been treated for an intrapyloric ulcer, with gastric retention, for eight years. A total of 1,350 r (depth dose) had been directed to the fundus and body of the stomach for the purpose of reducing

gastric acidity Six gastroscopies, prior to transabdominal vagotomy and gastroenterostomy, initially revealed mild to moderate hemorrhagic, hypertrophic, gastritis, slight atrophy developed during the irradiation Twenty-one months after operation the gastric mucosa appeared normal

CASE 25—A N, a housewife aged 67, had undergone a transabdominal vagotomy and, two months later, the local excision of a benign gastric ulcer A pronounced hourglass deformity of the stomach, with gastric retention, developed subsequently Gastroscopy three months after vagotomy revealed a normal mucosa in the upper portion of the stomach, the lower segment was not visualized, because of the greatly narrowed lumen

CASE 26—E T, a housewife aged 45, had experienced ulcer distress since 1922 A gastroenterostomy had been performed in 1932 The normal continuity of the bowel was reestablished in January 1945 Roentgen irradiation had been directed to the stomach, but the amount given and the effect on gastric secretion could not be ascertained, the patient first appeared at the University Clinics two and one-half years later Roentgenoscopy demonstrated a gastric ulcer, and a transabdominal vagotomy was performed After operation, the result of the insulin test was negative, and the nocturnal gastric secretion was greatly reduced The gastric ulcer was not demonstrable roentgenologically three months later The patient remained well for eighteen months, ulcer distress then reappeared The insulin test again yielded a negative response Free acid was present in the gastric contents after histamine stimulation Gastroscopy demonstrated a superficial ulcer on the lesser curvature, above the angulus The gastric rugae appeared normal, moderate atrophy had occurred in the midportion of the stomach Active peristalsis was observed in the antrum Gastric resection was performed eight days later, the distal third of the stomach being removed, the microscopic features are described later in this paper

Comment Gastric retention was observed in 6 of the 8 patients of this group treated by vagotomy alone The early observations in case 22 were incomplete in this regard, however, retention was not present four years and eight months after operation Gastric retention was not present in 1 patient undergoing both vagotomy and gastroenterostomy or, eighteen months after operation, in another patient treated by vagotomy alone Peristaltic activity was noted gastroscopically in 6 patients Gastritis of varying types and severity had been observed gastroscopically in the 7 patients examined before vagotomy Five had had irradiation directed to the upper portion of the stomach at varying intervals (usually of several years) prior to the operation The inflammation had not changed significantly in 5 patients, the condition had apparently subsided in 1, and slight improvement was noted in another

Control observations were not obtained in case 25, but a normal mucosa was observed after vagotomy, moderate localized atrophy was noted in case 26

The gastric ulcers healed in all 9 patients, in 1 instance within two weeks after operation However, a large ulcer was demonstrable in case 21, slightly more than three years after vagotomy In case 22 the

ulcer recurred temporarily eight months after operation, and an erosion was noted four and three-quarters years after vagotomy. A superficial ulcer was noted gastroscopically in case 26, eighteen months after vagotomy. The insulin test was performed after operation on eight patients, with negative results in 7 and a positive response in 1 (case 25).

Miscellaneous—CASE 27—M. S., a woman aged 45, with vague abdominal symptoms, was subjected to a transabdominal vagotomy in an unsuccessful effort to relieve the discomfort. Gastroscopy fourteen months later demonstrated a normal mucosa and active peristalsis. The result of the postoperative insulin test was negative.

General Comment—The present observations indicate that vagotomy does not alter significantly the gastroscopic appearance of the stomach. The mucosa seemed relatively unchanged in 13 of the 18 patients examined before and after operation, the original diagnoses had been normal mucosa in 5 cases, superficial gastritis in 3, hypertrophic inflammation in 2 and mixed gastritis in 3. An essentially normal mucosa was observed after vagotomy in 5 cases, of which the preoperative impressions had included hypertrophic gastritis, in 3, and superficial and mixed gastritis, in 1 each. The significance of this apparent improvement seems questionable, however, in view of the unpredictable variations in the type and severity of gastritis encountered spontaneously.⁶ An additional factor may be the individual differences in gastroscopic interpretation, recently emphasized by McGlone,⁷ although the majority of the postvagotomy examinations were made by one of us (J. B. K.), five physicians had participated in the preoperative studies.

In the present series, the prolonged retention of food and mucoid material apparently did not predispose to gastritis, nor did it seem to intensify a preexistent inflammation, as determined gastroscopically. The results of this study are in general agreement with the observations of Paulson and Gladsden.⁴ Asher⁵ concluded, however, that vagotomy produced definite gastritic changes, these occurred with less frequency when a gastroenterostomy was established in addition to the section of the vagus nerve. The rather high incidence of hypertrophic gastritis and superficial erosions in Asher's study is of interest. In contrast, the incidence and severity of gastritis in the present investigation did not differ significantly in relation to the presence or absence of gastroenterostomy; hypertrophic changes were not commonly encountered. However, recurrent ulcers were noted after vagotomy in 4 patients (cases 4, 13, 21 and 26). In case 22 erosions were observed in the orig-

6 Maimon, S. N., and Palmer, W. L. Chronic Gastritis. Observations on Its Course and Significance, *Gastroenterology* **6** 511, 1946.

7 McGlone, F. B. Observations on Gastritis Based upon Experience in a General Hospital in the South Pacific, *Gastroenterology* **10** 681, 1948.

inal area of the ulcer at intervals of twenty-two months, twenty-three months and four years eight months after vagotomy, erosions had also been noted before operation. In several patients the gastric mucosa appeared hemorrhagic at times, both before and after vagotomy. The histologic appearance of the stomach after vagotomy, as will be described later in this paper, usually did not differ strikingly from that observed in patients with ulcer having intact vagus nerves and in persons with no history of gastrointestinal disease.

With regard to prolonged gastroscopic observation, 5 patients (cases 4, 21, 22, 23 and 24) reexamined from twenty-one months to four years and eight months after vagotomy manifested active peristalsis, although a varying degree of retention was present in 3. Gastritis persisted in 3 and apparently subsided in 2 of 4 patients on whom gastroscopy was performed only after vagotomy, at postoperative intervals of eighteen months or more, a normal mucosa, localized atrophy and superficial gastritis were observed in 1 each, and both a normal mucosa and mild superficial changes in 1.

HISTOLOGIC APPEARANCE OF STOMACH AFTER VAGOTOMY

The stomach was examined histologically after vagotomy in 11 patients. The observations are presented in individual case reports.

CASE A—O K, a 59 year old housewife with diabetes and hypertension, experienced pain from an ulcer for three weeks. Roentgenoscopic examination disclosed a duodenal ulcer, and symptoms were relieved by medical treatment. The patient first appeared at the University Clinics one year later, because of recurrent distress. A transabdominal vagotomy and posterior gastrojejunostomy were performed after one month. However, the patient died of atelectasis and pneumonia one week after the operation, despite bronchoscopic aspiration and the administration of penicillin. At autopsy, the vagotomy anatomically appeared complete. A large, healing ulcer was present in the duodenal bulb. Additional diagnoses included severe arteriolosclerosis and arteriosclerosis of the pancreatic vessels, severe fibrosis and atrophy of the pancreas, bilateral bronchopneumonia of the lower lobes, acute purulent bronchitis, severe generalized arteriolosclerosis, moderate arteriosclerosis and hypertrophy of the left ventricle. The gastric mucosa presented no gross abnormality. Histologic examination demonstrated an essentially normal mucosa, with minimal cellular infiltration. The gastric glands and crypts were well preserved. The parietal and chief cells were abundant and appeared normal.

CASE B—M C, a 54 year old woman, had experienced ulcer distress for ten years. Roentgenoscopic examination demonstrated a benign gastric ulcer, the ulcer was excised and a vagotomy performed. A biopsy of antral mucosa adjacent to the ulcer disclosed moderate chronic gastritis. A posterior gastroenterostomy was established several weeks later because of obstruction. The patient died of a reaction to the infusion of plasma one month after vagotomy. Autopsy disclosed hemoglobin precipitate in the renal tubules. The vagotomy appeared anatomically complete. The pylorus was almost completely obstructed by a mem-

brane composed of gastric mucosa on the superior surface and duodenal mucosa on the inferior surface, the channel through this valvular shelf measuring 2 mm in diameter, this deformity seemed attributable to the local excision of the ulcer. Grossly, the gastric mucosa appeared smooth, but otherwise normal. Microscopic examination of the mucosa of the fundic and prepyloric regions disclosed a minimal gastritis, a few cystic glands, hypertrophy of occasional muscle fibers and congestion of the submucosal veins. The parietal and chief cells were normal. Acid-secreting cells were present also in glands on the duodenal border of the pylorus.

CASE C—F K, a 59 year old woman, on roentgenoscopic examination presented a small ulcer on the lesser curvature of the stomach and narrowing of the antrum. Gastroscopy disclosed mild superficial gastritis. A transabdominal vagotomy and posterior gastroenterostomy were performed two weeks later. Microscopic examination of a specimen from the fundus of the stomach indicated minimal chronic gastritis, the cellular infiltrate consisting chiefly of plasma cells and eosinophils (fig 1A). The parietal and chief cells were normal in appearance and distribution (fig 1B). The patient died five months later of a glioblastoma multiforme of the left temporal lobe. Autopsy revealed, in addition, lipid bronchopneumonia and an acute gangrenous abscess in the lower lobe of the right lung. Anatomically the vagotomy appeared complete. Grossly, the gastric mucosa, except for the scar of a healed prepyloric ulcer, was normal. Striking changes were observed microscopically, in comparison with the appearance of the control biopsy specimen obtained five months earlier. The stomach now was involved diffusely by an unusually severe, chronic gastritis, most pronounced in the antrum (fig 2), there was much interstitial infiltration of the entire gastric wall, chiefly by round cells. Cystic changes were prominent, but so-called intestinalization was not present, the thickness of the mucosa was approximately normal. Of particular interest were the pronounced hyperchromatism of glands and the significant decrease in number of acid-secreting cells, these cells in many areas were poorly differentiated and difficult to identify (fig 3).

CASE D—G S,⁸ a 46 year old man, underwent a partial gastrectomy after twenty years of recurrent distress from a duodenal ulcer, a jejunal ulcer developed several weeks later. The ulcer healed after transthoracic vagotomy but recurred six months later, complicated by a gastrojejunal fistula. The fistula was repaired, and several previously uncut vagus fibers were excised. However, the secretion of hydrochloric acid remained excessive. The patient died of a massive hemorrhage, five days after the second operation and six and one-half months after the initial vagotomy. Autopsy revealed an ulcer crater, 8 by 5 cm, at the margin of the gastroenterostomy site, with an eroded artery in its base. No intact vagus fibers were grossly visible, but apparently viable nerves were identified histologically between the muscle layers of the esophagus and the stomach. The pancreas contained an islet cell carcinoma, one metastatic lesion was present in the liver. Grossly, the gastric mucosa appeared normal. Histologic examination disclosed rather severe superficial gastritis and occasional cystic glands. The parietal and chief cells were abundant and well preserved. This case was described in more detail in another paper.⁸

CASE E—R B, a 66 year old man, had experienced symptoms referable to the gastrointestinal tract for thirty years and known ulcer distress for twenty years.

⁸ Kirsner, J. B., Levin, E., and Palmer, W. L. Observations on the Excessive Nocturnal Gastric Secretion in Patients with Peptic Ulcer, *Gastroenterology* 11: 598, 1948.

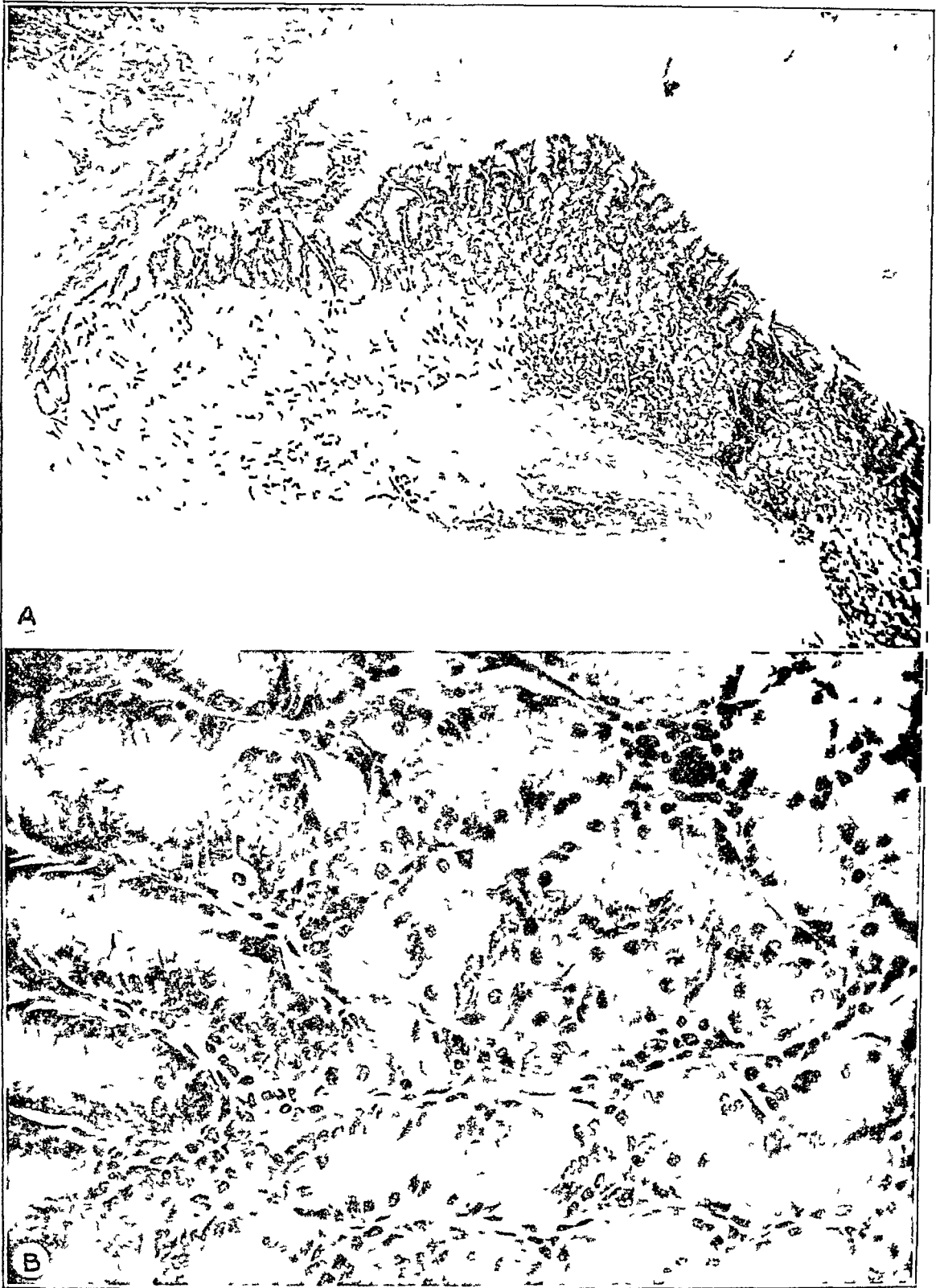


Fig 1 (case C)—Biopsy specimen of mucosa of the fundus of the stomach, taken at the time of vagotomy. *A*, minimal gastritis, preservation of the normal glandular pattern ($\times 62$). *B*, numerous normal-appearing parietal cells in an essentially normal gastric mucosa ($\times 310$).



Fig 2 (case C)—Gastric mucosa at autopsy, five months after vagotomy. Above, fundic mucosa, severe, chronic gastritis with cystic glands, the loss of the mucus-secreting layer is a postmortem artefact. Below, antral mucosa, severe, chronic, cystic gastritis. $\times 50$

A transabdominal vagotomy was performed at another hospital, but symptoms recurred within two weeks. Roentgenoscopic examination disclosed an ulcer crater in an undeformed duodenal bulb, and a second vagotomy, together with an anterior gastroenterostomy, was accomplished. Complete obstruction of the gastroenterostomy opening occurred after operation, necessitating side to side anastomoses in the jejunum and ileum. The patient died several days later, after a reaction to the administration of pooled plasma, death occurred one year after the initial operation and fifteen days after the second vagotomy.

Autopsy indicated that the vagotomy was complete anatomically. The only evidence of the former duodenal ulcer consisted of a focus of epithelium, 1 cm in diameter, thinner than the surrounding mucosa, from which folds radiated.

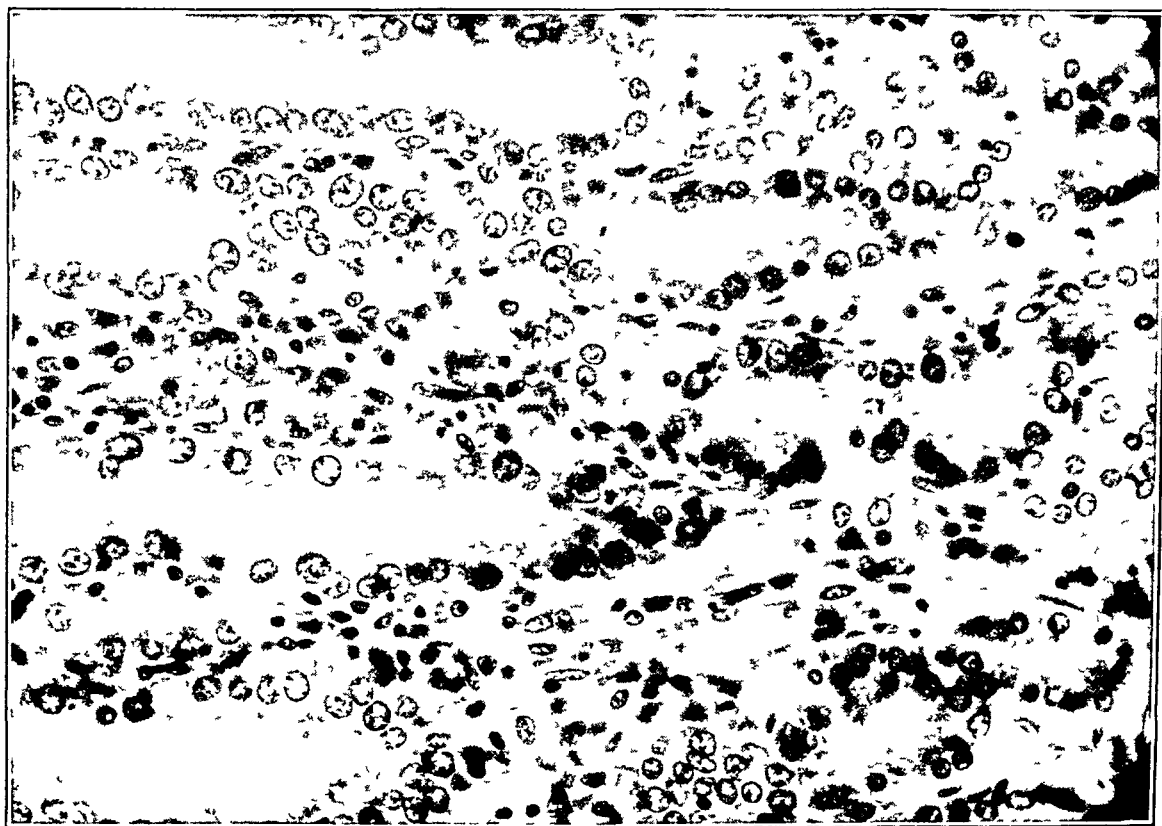


Fig 3 (case C) —Fundic mucosa at autopsy. Most of the parietal cells have disappeared, the glands are lined with a simplified type of epithelium. $\times 350$

Additional diagnoses included massive aspiration pneumonia of the upper and middle lobes of the right lung, pulmonary edema and thrombosis of the mesenteric veins. The gastric mucosa contained minute erosions and hemorrhages and appeared edematous in the region of the gastroenterostomy wound. Histologically, the mucosa appeared essentially normal, with only minimal interstitial infiltration with round cells. One small area of mild atrophy was noted on the lesser curvature. Parietal and chief cells were abundant and appeared normal.

CASE F—E. M.,⁸ a 63 year old man, had required closure of a perforated duodenal ulcer one year after the onset of symptoms. Ulcer distress recurred, and a transabdominal vagotomy and posterior gastroenterostomy were performed one

year later. A jejunal ulcer developed within six months, the result of the insulin test was positive. A second vagotomy was then accomplished, with the excision of a large fiber in the posterior wall of the esophagus and of smaller branches below the esophagus. Roentgen radiation, a total of 1,656 r (depth dose), was applied to the fundus and body of the stomach for the purpose of reducing gastric acidity. The result of the insulin test remained positive and the output of hydrochloric acid excessive. Ulcer distress recurred several months later, and a fourth operation was performed, at which time a large jejunal ulcer perforated spontaneously. The jejunum containing the anastomosis and the perforation was resected, and an end to end jejunostomy was established. The patient was readmitted to the hospital three months later, because of several mild hematemeses, and died soon thereafter, of a "toxic reaction," one year and three months after the initial vagotomy and six months after the second vagotomy.

Autopsy demonstrated intact vagus fibers passing along the esophagus into the stomach. The duodenal ulcer was healed. Additional findings included mild toxic encephalopathy of the cerebral cortex, bronchopneumonia with early abscess formation, a benign hepatoma and an old occlusion of the right coronary artery. The gastric mucosa contained multiple petechial hemorrhages. Histologic examination disclosed only minimal cellular infiltration, no evidence of atrophy was noted. The parietal and chief cells were numerous and well preserved.

CASE G—S. K., a 39 year old man, had experienced ulcer distress for twelve years, a duodenal ulcer was demonstrated roentgenologically. The symptoms were relieved completely and the patient gained approximately 30 pounds (13.6 Kg.) in weight after a transabdominal vagotomy. No free acid was present in the nocturnal gastric secretion. Results of insulin tests, made after operation and eighteen months later, were negative. The patient died of bullet wounds approximately eighteen months after operation.

At autopsy, no intact vagus fibers were grossly visible. Small, nonmyelinated, apparently normal nerve trunks were observed histologically in the periesophageal tissues, several of these fibers were buried deeply in the muscle layers of the esophagus. Grossly, the stomach appeared normal except for slight localized thinning of the mucosa near the pyloric ring. The gastric wall was involved diffusely by a rather severe gastritis, with pronounced cellular infiltration, predominantly of lymphoid cells, this was most pronounced in the superficial zone, but in many areas the infiltrate reached and penetrated the muscularis mucosae. Large and small lymphoid follicles were situated along the muscularis mucosae. Cystic glands and focal atrophy of the mucosa were observed near the cardiac orifice. The mucosa elsewhere was not atrophic. The mucosa of the fundus was thick and contained many normal-appearing parietal and chief cells. The condition of the gastric pits could not be evaluated because of the postmortem loss of epithelium. Toward the antrum, the exudate was more pronounced, an occasional cystic gland was noted. Considerable adipose tissue was present in the submucosa of the pyloric ring and in the submucosa of the entire small intestine. The first portion of the duodenum contained several areas of scarring, with regeneration of the surface epithelium and of Brunner's glands.

CASE H—N. K., a 51 year old man, had experienced ulcer distress for eight years. Roentgenoscopic examination demonstrated an ulcer crater in a deformed duodenal bulb. Roentgen radiation, a total dose of 1,671 r, was applied to the fundus and body of the stomach. The ulcer recurred eight months later, and a transthoracic vagotomy was performed. Gastroscopy, performed one week before operation, had demonstrated an extensive hypertrophic gastritis involving the body

and antrum of the stomach. The result of the postoperative insulin test was negative. The ulcer healed and did not recur. The patient died two years and three months later, of extensive metastases from a chondrosarcoma of the left tibia. Autopsy demonstrated lesions in the left hip, regional and retroperitoneal lymph nodes, kidneys, liver, diaphragm, heart, thyroid, lungs, ribs and cranium. There were no intact vagus fibers grossly, histologic examination, however, indicated the presence of nerve fibers. The upper two thirds of the stomach appeared normal in size, shape and tone, the distal third, however, was contracted to approximately the caliber of the first portion of the duodenum. The pylorus was normal. The duodenal ulcer was healed. Multiple hemorrhages had occurred in the gastric mucosa, the rugae appeared somewhat flattened. Histologic examination disclosed minimal superficial gastritis in the fundus, slight thinning of the mucosa of the lesser curvature and early atrophy and slight round cell infiltration of the mucosa adjoining the pylorus. The parietal and chief cells were abundant and well preserved.

CASE 13—Clinical details in this case have been recorded previously. A partial gastric resection was performed five and one-half months after vagotomy for a duodenal ulcer. The distal half of the stomach was removed, a benign ulcer was present on the lesser curvature, 7.5 cm above the pylorus. Because of adhesions it was not possible to determine the presence or absence of intact vagus fibers anatomically, however, the insulin test had yielded a negative acid response. The stomach was involved irregularly by moderately severe gastritis, with infiltration of plasma cells and eosinophils and scattered lymphoid follicles. Accumulations of leukocytes, including polymorphonuclear cells, were present in numerous crypts. The mucous cells on the surface were well preserved. Focal thinning of the mucosa had occurred in the uppermost portions of the resected specimen, and the glands in these areas were shortened. Most regions, however, contained numerous, normal-appearing parietal and chief cells. The mucosa near the entrances of the gastric pits was normal, at deeper levels the glands appeared hyperchromatic, and the cells were crowded, the cellular density being interpreted as compatible with very early atrophy of the gastric mucosa.

CASE 26—Clinical features in this case have been summarized earlier in this paper. A gastric resection was performed eighteen months after transabdominal vagotomy, the distal third of the stomach, containing a small erosion on the posterior wall, was removed. The gastric rugae grossly appeared normal. Histologic examination revealed a relatively normal mucosa. The gastric glands and crypts were well preserved, slight fibroplasia was evident at the bases of the glands. There was a minimal amount of cellular infiltrate, slightly more being present in the antrum. The mucous cells were well preserved. The parietal and chief cells were abundant and appeared normal. Glands bearing both acid and peptic cells, intermixed with seromucinous glands, were observed to extend to the pyloric ring.

CASE 4—Clinical features of this case have been described. A large, benign ulcer developed four years and three months after transthoracic vagotomy for a duodenal ulcer. The result of the insulin test was positive. A partial gastric resection was performed, and an intact vagus fiber was severed. Histologic examination disclosed diffuse chronic gastritis, most pronounced in the region of the ulcer and characterized by increased cellularity of the stroma and by small numbers of leukocytes in the lumens of the glands. The cellular infiltrate in many areas extended into the muscularis mucosae. There were many basally located mucosal lymphoid nodules, especially near the ulcer. Minimal atrophy was present. The parietal, chief and mucous cells were abundant and well preserved.

Comment—The histologic appearance of the stomach after vagotomy in 9 of the 11 patients did not differ from that often observed in patients with peptic ulcer and with intact vagus nerves, and, indeed, in persons with no history of gastric disease. The vagotomy appeared complete anatomically in 4 of the 8 bodies examined at autopsy and incomplete in 4. No unusual atrophy of the mucosa had taken place. The parietal and chief cells were normal in appearance and distribution. Evaluation of the mucus-secreting cells was possible only in the 3 patients undergoing gastric resection, in these they appeared normal.

Extensive round cell infiltration, conspicuous cystic formation and degeneration and diminution in the number of acid-secreting cells were observed in 1 patient (case C) five months after complete vagotomy. The relation of these changes to the vagotomy is difficult to evaluate conclusively in view of the concomitant presence of a brain tumor and the various complicating infections. However, in our experience, the degeneration and disappearance of parietal cells are rare in a mucosa of normal thickness. The gastritis in cases G and 13 and the erosions in case E seemed more pronounced than is usual, however, similar changes have been observed occasionally in patients with ulcer and intact vagus nerves and in persons with no history of gastric disease. The increased amount of fat in the submucosa of the pylorus and the entire small intestine in S. K. is of interest, the significance of this observation and its relation to the vagotomy are not clear at present. In general, the histologic evidence, in support of the gastroscopic results, suggests that vagotomy usually does not produce striking changes, either grossly or microscopically detectable, in the appearance of the stomach.

Two additional observations are of interest. In case H, two years and three months after vagotomy, the distal third of the stomach was contracted to the diameter of the duodenum, and the cardiac and pyloric orifices were normal. Multiple hemorrhages were present in the gastric mucosa of 2 patients, and hemorrhages and minute erosions in 1 patient, these probably represent antemortem changes, not attributable to the vagotomy.

CONCLUSIONS

- 1 Vagotomy usually does not alter significantly the gastroscopic appearance of the gastric mucosa.

- 2 Peristalsis frequently is observed in the antrum after vagotomy. However, gastric retention persists for a time in most patients without gastroenterostomy.

- 3 The prolonged retention of food and mucoid material apparently does not cause gastritis or accentuate preexistent gastritis.

- 4 Benign gastric ulcer may develop or recur from several months to several years after vagotomy.

5 The histologic appearance of the stomach at intervals of one week to four years and eight months after vagotomy usually does not differ significantly from that often observed in patients with ulcer and intact vagus nerves, and in persons with no history of gastric disease. No unusual atrophy occurs, and the parietal and chief cells are normal in appearance and distribution.

6 Rarely, severe gastritis and degeneration of the acid-secreting cells may be observed after vagotomy, in the 1 such case in this series, the relation of the changes to the operation could not be evaluated conclusively because of the presence of concomitant disease.

HYSTERICAL TYPE OF NONGASEOUS ABDOMINAL BLOATING

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IN 1911, I saw a psychopathic woman, past the menopause, who, with her protuberant abdomen, was sure that she was pregnant by the Holy Spirit. She insisted on going to a lying-in hospital and was outraged when told that she was not going to have a baby. I learned then that a bloated abdomen can be produced purely by nervous means. Later I saw an occasional nervous, unhappy woman who during the day would become more and more bloated, until by evening she would appear about eight months pregnant. The abdomen usually became flat during the night. Soon I began to realize that in these cases the cause could not be gas. Why? Because (1) a roentgenogram of the enlarged abdomen showed that there was no excess of gas in the stomach or bowel, and (2) as the swelling went down, sometimes suddenly, there was no passage of flatus.

That there was no causative organic disease in the abdomen was indicated by the fact that in almost every case several exploratory operations had failed to reveal anything significant. Usually the appendix, uterus and gallbladder had been removed, without avail. One woman with a particularly stormy form of this syndrome, whom I saw with Dr. Bargen, had had her abdomen opened so many times that she had finally lost count.

I now report 92 cases of this neurotic or hysterical type of non-flatulent bloating. The syndrome is similar to that described in the past under the terms "phantom tumor," "pseudoileus" or "accordion abdomen." There are several varieties of the syndrome, some severe, painful and disabling, and others in which the distention is mild or occasional or incidental to more serious troubles. Doubtless many neurotic women occasionally bloat in this way but have so little trouble with the syndrome that they do not mention it when they go to an internist.

DEFINITION AND CLINICAL PICTURE

The essential point in all the cases described here is that the pronounced bloating is due not to any excess of gas in the digestive tract but apparently to a contraction of the muscles lining the back and the

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* A preliminary report on this subject was read at the Sixtieth Session of the Association of American Physicians, Atlantic City, N. J., May 6, 1947, and was published (*Tr. A. Am. Physicians*, 60:86, 1947).

upper end of the abdominal cavity. Sometimes, in addition, there may be a relaxation of the muscles of the anterior abdominal wall. These changes, associated often with the assumption of an extremely lordotic posture by the patient, tend to throw the abdominal contents forward and somewhat downward, toward the brim of the pelvis. In one instructive case, the woman, while standing in my office, would take off a 2 inch (5 cm) belt and instantly bloat, apparently by relaxing the anterior abdominal wall. In this instance there was no simultaneous increase in lordosis. Then the patient would put the belt on loosely, with this form of autosuggestion the muscles would contract, and the abdomen would appear normal again.

Most patients stated that at first they tended to bloat only once in months or in a year. Later the interval shortened, until the bloating sometimes came every day. This shortening of the interval is typical of those types of abdominal "storm" for which no local cause can be found.

In most cases, the swelling develops quickly after a large meal, or slowly during the afternoon, and diminishes during the night without the passage of flatus. This is a most important point diagnostically. The patient is often well between spells, with good appetite and digestion. In rare cases, there is a picture of severe constipation, with what appears to be an attack of intestinal obstruction.¹

The Several Types of Bloating—Before going further, it may be helpful to note that there are a number of types of bloating, and that some nongassy bloaters on occasion have one or more of the other types of abdominal swelling. Unless this fact is recognized and, while taking a history, the physician unscrambles the several stories, he may become confused.

True gassy bloating due to indigestion can be produced by (a) eating too much, (b) eating when nervously upset, (c) eating indigestible or poorly prepared food, (d) eating foods such as baked beans, onions or cabbage which are notoriously gassy, (e) eating too much roughage or (f) eating a food to which one is allergically sensitive.

There is a type of bloating that appears with some forms of diarrhea, especially sprue or slight intestinal obstruction, in cholecystitis, in constipation, or with the swallowing of large amounts of air, as when the person is chewing gum.

Three other forms of bloating associated with much gas in the bowel are due (a) to the physical stimulus that comes from chewing or ingesting food, (b) to the stimulus derived from drinking a glass of cold

1 Christianson, H. W., and Barger, J. A. Functional Abdominal Distention Simulating Intestinal Obstruction, Proc. Staff Meet., Mayo Clin. 6: 441-448 (July 29) 1931.

water, pop or beer and (c) to taking a nap. Some persons bloat so suddenly after eating or drinking that the mechanism is obviously nervous, mechanical or physical. Insufficient time elapses for a chemical effect to take place.

CLINICAL MATERIAL

I began this study by making abstracts of some 150 case records of bloaters I had seen. As I analyzed the histories, it was apparent that in some 53 cases, the clinical picture was mainly that of true flatulence, with much gas in the bowel. The patient's illness was due for the most part to such troubles as indigestion, cholecystitis, food allergy or constipation. Helpful diagnostically was the fact that many of these truly gassy bloaters could be made more comfortable with an elimination diet, a daily enema or the removal of a diseased gallbladder; the neurotic bloaters here described could be helped little if at all by such measures.

The few cases which left me puzzled were those in which a patient with what appeared, in most spells, to be the neurosis of the abdominal wall described in this report also occasionally experienced food sensitization or an overly irritable bowel, which filled with gas when the patient drank cold water, pop or beer. After the latter type of bloating there was at times passage of some flatus. I excluded reports of most of these complicated cases from this paper because I wished to keep the picture of the neurosis of the abdominal wall as clearcut as possible. Eventually I kept reports of the 92 cases which have been used in the present study.

I regret that not all cases could be studied extensively and that only certain patients could be watched through several crises of bloating. Several were seen for only one consultation on a busy day, but all had had examinations to rule out organic disease of the abdomen. From all of them, I obtained the history which is diagnosis enough, namely, that of pronounced bloating diminishing without the passage of flatus. Because not all cases were studied with equal thoroughness, I cannot express the frequency of the several symptoms in percentages; I can give only estimates of frequency, or the number of cases in which I made note of a certain symptom.

SUDDENNESS OF BLOATING AND RECESSION

Significant and interesting is the suddenness with which the abdominal wall will often expand and occasionally contract. One woman said, "I go up and down like an accordion," and, curiously, Bernheim,² in 1891, and Kaplan,³ in 1900, wrote on *ventre en accordéon*. In regard to

2 Bernheim, H. Hypnotisme, suggestion, psychotherapie, Paris, O. Doyn, 1891.

3 Kaplan, L. De la pseudotympanite nerveuse, ou ventre en accordéon, Thesis, Paris, no. 30, 1900.

another patient, a physician wrote, "The abdomen bloats suddenly and dramatically." Twelve patients said that one form of bloating came within seconds after drinking cold water (the trigger mechanism), and 15 spoke of the suddenness with which they bloated after eating or drinking. Several bloated rapidly while in my office, there was no sign to indicate that they had swallowed air. Some of these patients had to keep on hand three sets of clothes, designed for three sizes of abdomen!

Kaplan³ told of a young man who learned the trick of bloating the upper half of his abdomen at will. He had discovered it accidentally but could not say just how it was done, he could also stop the bloating when desired. The expansion could be maintained for some time without fatigue. During this time, the boy could eat, drink even a liter of fluid, urinate or whistle.

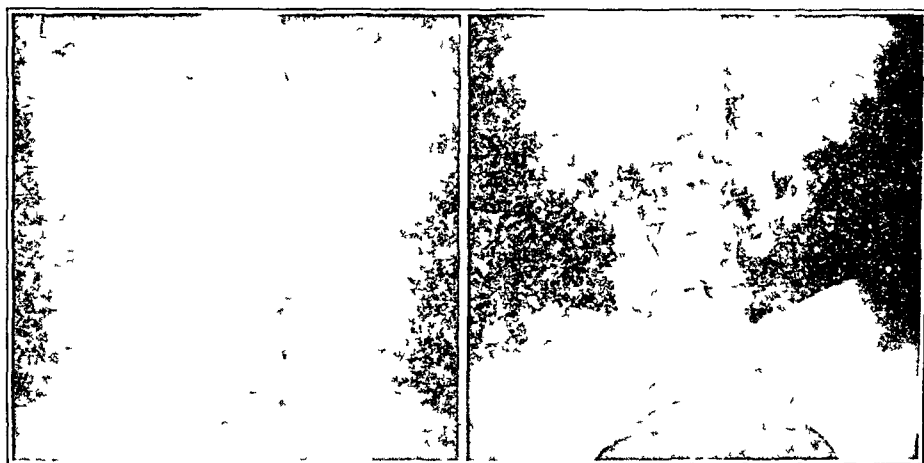


Fig 1—Roentgenograms made while patient was bloated. They show no excess of gas in the intestine.

ABSENCE OF GAS IN THE ABDOMEN

As already noted, an essential feature of this disease is the lack of any excess of gas in the bowel during the attacks of bloating. This was shown most convincingly by roentgenograms of the abdomen while bloating was present. Figure 1 shows how little gas was present in any part of the bowel of a typical patient.

Interestingly, one hundred years ago Sir James Y. Simpson⁴ described the syndrome and knew that it was not due to gas in the bowel. To demonstrate this fact to his students, he used to place a tube in the rectum of a patient, with the outer end in a glass of water. He would

⁴ Simpson, J. Y. *The Obstetric Memoirs and Contributions*, edited by W. O. Priestley and Horatio R. Storer, Philadelphia, J. B. Lippincott Company, 1855-1856, vol. 2, p. 101.

then give an anesthetic, and when the patient's abdomen suddenly became flat, he would call attention to the fact that no gas had come from the bowel. Janet is said to have noted this type of relief of bloating without the passage of gas. In 1881, Weir Mitchell⁵ reported the case of a bloater, a woman who knew that the swelling had nothing to do with gas, in her case, it was caused by emotion. In Goldschmidt's case,⁶ reported in 1922, roentgenograms showed no excess of gas in the patient's abdomen.

According to Kaplan,³ one hundred years ago in Europe, in cases of supposed intestinal obstruction, the patient's intestines used to be punctured with a trocar. In this way it was learned that no gas was present in the cases of hysterical bloating.

MECHANISM OF BLOATING

Years ago it became clear to me, as it had to others, that in the case of the type of bloater described, the distention could not be due to gas. The next question was whether it could be due to massive angioneurotic edema of the intestine.

Edema—Somewhat in favor of the theory of edema as a causative factor is the fact that in 16 of the cases reported in the present study, the patient tended at times to become slightly edematous, the swelling occurring all over the body or in the hands, feet or eyelids. In no case could the edema be blamed on any disease of the heart or kidneys. After a time, I saw that edema of the bowel could hardly be the explanation for the distention because of the rapidity of the rise and fall of the abdomen. Insufficient time elapsed for any change to occur in the volume of its contents.

Sudden Deflation—On several occasions, I saw an abdomen deflate without the passage of flatus either instantly on, or a few minutes after, (1) the induction of spinal or general (ether) anesthesia or of anesthesia with thiopental sodium U S P (pentothal sodium®), (2) the blocking of the splanchnic nerves with an injection of procaine hydrochloride U S P, (3) the onset of an attack of vomiting or (4) the reception of a hypodermic injection of morphine. In 1 case, the abdomen would promptly contract when the girl assumed the knee-chest position, and in many others, it deflated entirely, or nearly so, when the woman lay on her back, especially with the thighs flexed on the abdomen. In 1 patient under spinal anesthesia, the abdomen suddenly deflated the moment the anesthesia reached the nipples.

5 Mitchell, S. W. Lectures on Diseases of the Nervous System, Especially in Women, Philadelphia, H. C. Lea's Son & Company, 1881, pp. 186-188.

6 Goldschmidt, W. Ein 4 mal als Ileus laparotomierter Grenzfall von Spasmodismus und Hysterie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 35: 544, 1922.

Because I could not imagine any way in which the volume of the abdominal contents could be so suddenly restored to normal, I concluded that no increase took place in the volume of the abdominal contents. In some cases I gained this impression also from measuring the girth of the woman's abdomen before and during bloating.

Among the writers in the past who commented on the rapidity with which the "tumor" disappeared when the patient was anesthetized, and with which it returned when she awoke were Priestley (in 1858), Wells,⁷ Luton,⁸ Simpson,⁴ Gowers,⁹ McArdle and Kolipinski,¹⁰ Krukenberg,¹¹ Talma,¹² Kaplan,³ McDonnell,¹³ Da Costa,¹⁴ Ramskill and Jones,¹⁵ Haultain,¹⁶ Kerr and Ferguson,¹⁷ Purves-Stewart¹⁸ and Garrigues¹⁹

Lordosis—Other important observations made early in the investigation were that at least 11 of these patients were more than usually lordotic when bloated, and that this factor had much to do with pushing the abdominal contents forward. Osler,²⁰ Gowers,⁹ and Bagen and others²¹ noted this "arching forward of the spine", it was also shown, in 1884, by Krukenberg,¹¹ whose illustrations are reproduced here in figure 2. The woman was bloated because of her lordosis, when she straight-

7 Wells, T. S. *Diseases of the Ovaries: Their Diagnosis and Treatment*, London, J. Churchill & Sons, 1865, vol. 1.

8 Luton, cited by Kaplan.³

9 Gowers, W. R. *A Manual of Diseases of the Nervous System*, Am. ed. Philadelphia, P. Blakiston's Son & Co., 1888.

10 McArdle, T. E., and Kolipinski, L. *A Summary of the Published Cases of Phantom Tumor of the Abdomen, and the Etiology of that Condition and of Spurious Pregnancy*, New York State J. Med. **43** 595, 1886.

11 Krukenberg, G. *Zur Kenntniss der hysterischen Phantomgeschwulste*, Arch. f. Gynak. **23** 139, 1884.

12 Talma, S. *Zur Kenntniss der Tympanitis*, Berl. klin. Wchnschr. **23** 369, 1886.

13 McDonnell, cited by McArdle and Kolipinski.¹⁰

14 Da Costa, J. M. *Medical Diagnosis with Special Reference to Practical Medicine: A Guide to the Knowledge and Discrimination of Diseases*, ed. 2, Philadelphia, J. B. Lippincott Company, 1866, p. 541.

15 Ramskill and Jones, cited by McArdle and Kolipinski.¹⁰

16 Haultain, F. W. N. *Spurious Pregnancy: A Critical Treatise from a Practical Experience*, Am. J. M. Sc. **101** 342, 1891.

17 Kerr, J. M. M., and Ferguson, J. H. *Combined Text-Book of Obstetrics and Gynecology*, New York, William Wood & Company, 1923.

18 Purves-Stewart, J. *The Diagnosis of Nervous Diseases*, ed. 9, Baltimore, Williams & Wilkins Company, 1945, p. 661.

19 Garrigues, H. J. *A Text-Book of the Science and Art of Obstetrics*, ed. 2, Philadelphia, J. B. Lippincott Company, 1907.

20 Osler, W. *The Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine*, ed. 3, New York, D. Appleton & Co., 1898.

21 Bagen, J. A., Adson, A. W., Lundy, J. S., and Dixon, C. F. *Functional Abdominal Distention Simulating Megacolon*, Am. J. Digest. Dis. **3** 17, 1936.

ened her spine under anesthesia or voluntarily, the bloating disappeared I suspect that with a little practice, any one with good muscles and a limber spine could push the anterior abdominal wall forward, just as he can pull it in until it is scaphoid (fig 3)

That lordosis often is an important factor can be shown, as already noted, by having the bloated patient lie down (figs 4 and 5) Especially when the knees are flexed on the abdomen, the woman will usually lose much, or all, of the bloated appearance When she is placed on her side

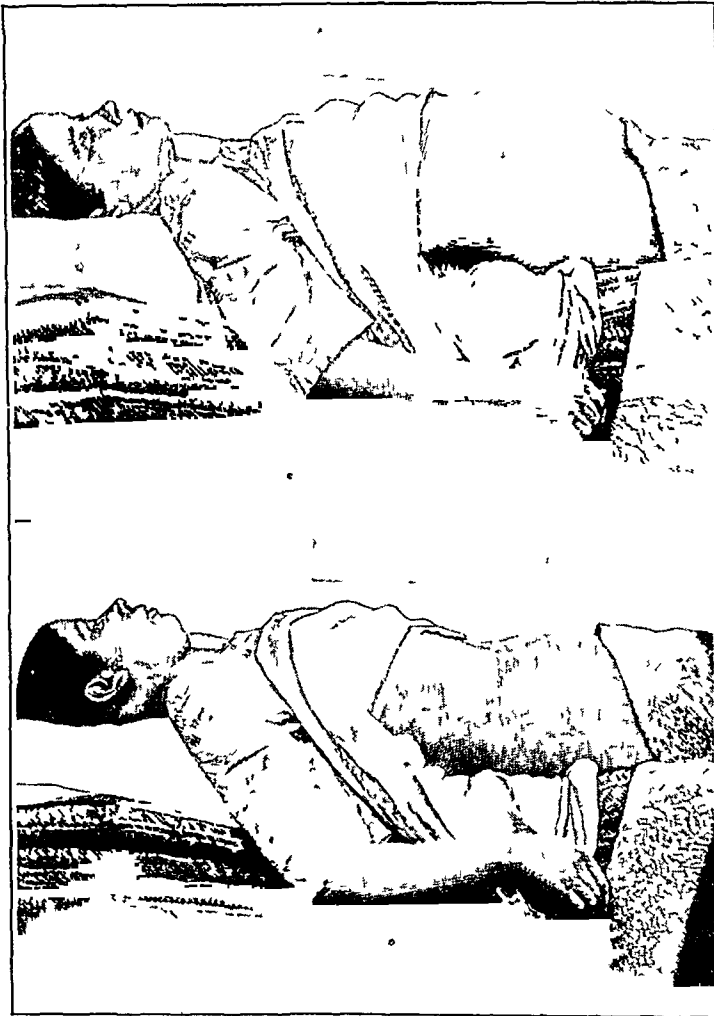


Fig 2—When the girl was bloated she was lordotic, when she slumped, either voluntarily or under the influence of chloroform, the bloating disappeared (From Krukenberg¹¹)

and the thighs are quickly flexed on the abdomen the lordosis is even better overcome, and a distended abdomen is likely to deflate and become soft When the woman gets up and slumps into her old lordotic posture, the bloating usually returns (fig 6) For years Bargaen has been using this doubling up of the patient as a diagnostic procedure, if the abdomen becomes flat, he knows what type of bloating is present Krukenberg used much the same technic in 1884

It would seem that in pushing the abdominal contents forward, bloating should be facilitated by the simultaneous relaxation of the muscles of the anterior abdominal wall. Sometimes the muscles are relaxed, but sometimes they are contracted, tense and hard. In 1 case (reported by me in 1945²²), in which the syndrome was, I believe, a variant of the one described in this report, the patient's contracted, boardlike abdominal wall was always flat. Perhaps the flatness of the abdomen was due partly to the contraction of the muscles of the anterior abdominal wall, and partly to an absence of a forward thrust from the muscles at the back.

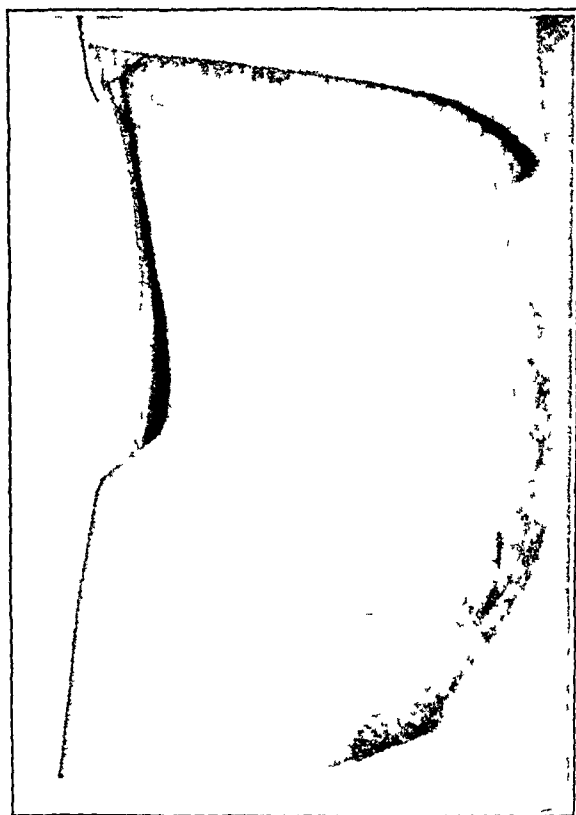


Fig 3—Lordosis producing the appearance of bloating (From Bargaen, Adson, Lundy and Dixon²¹)

That lordosis is not an essential factor in the bloating was obvious in some cases. For instance, lordosis does not appear to have had anything to do with the tremendous bloating of the woman whose abdomen was pictured by Vaughn²³ (fig 7). She bloated when her hand was placed in ice water and the abdomen deflated when the hand was

22 Alvarez, W. C. A Rare Syndrome of Crisislike Abdominal Pain, *Gastroenterology*, 4:296, 1945

23 Vaughn, W. T. *Practice of Allergy*, St. Louis, C. V. Mosby Company 1939

warmed again Long ago Simpson¹ noted that in some cases lordosis was not a factor

Significance of Contractions or Bloating of a Part of the Abdominal Wall—A feature which helped convince me that this syndrome is due primarily to spasm of the muscles of the abdominal wall was the observation of several cases in which the bloating, like a phantom tumor, involved only half the patient's abdomen, or even only one quadrant of it

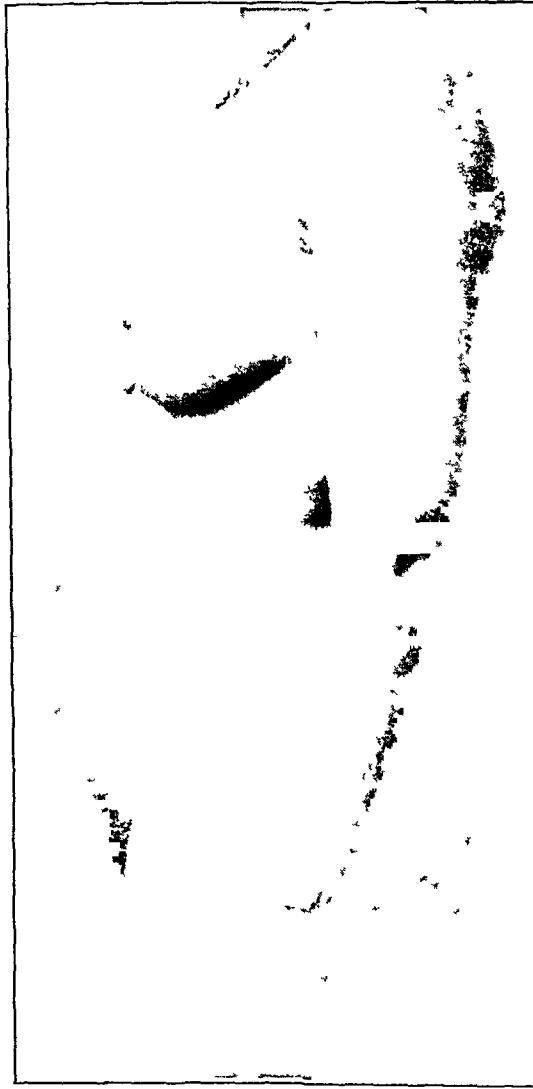


Fig 4—A slightly bloated woman, with some lordosis

In 1 case, the bloating would begin in the left lower quadrant Then, by bending and twisting in a certain way, the patient could, as she said, "throw the tumor over" into the right lower quadrant, it might then suddenly disappear I saw her one day when she was bloated only in the right lower quadrant Two women bloated only on the right side, with a contraction of the abdominal muscles on that side, one day I watched 1 of them as she bloated on only the left side One woman

bloated only in the upper half of the abdomen and 1, only in the lower half. Another would bloat first above the navel, the swelling would then spread into the lower half of the abdomen. Swelling in the case of another woman would begin with a contraction of the abdominal muscles in the left upper quadrant, the patient then would bloat over the entire abdomen.

In a few instances, segments of only one rectus abdominis muscle would go into spasm to such a degree that some physicians who saw the patients thought they were dealing with a tumor. A nervous man with this condition was one day rushed to a hospital by his surgeon for removal of a supposed cancer of the cecum. Fortunately, the man's brother insisted on a consultation. When I first saw the patient, the tumor was obviously in the lower half of the right rectus muscle, but

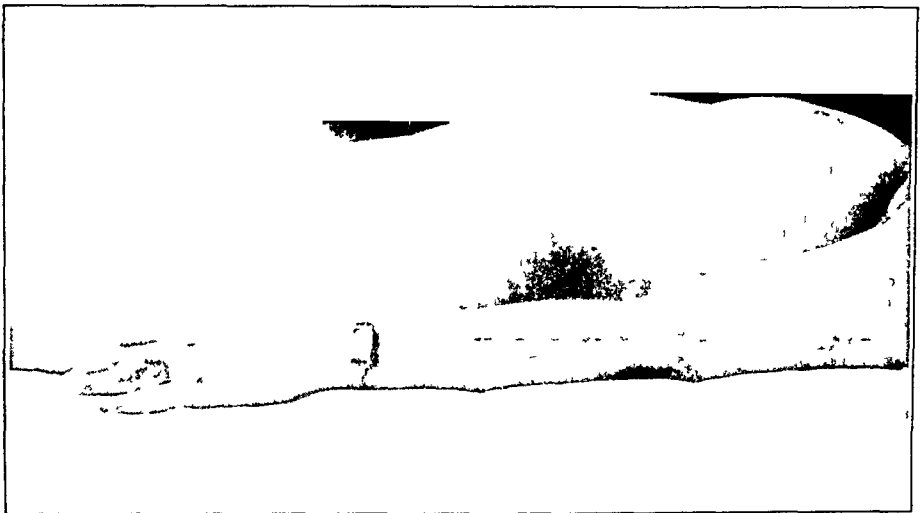


Fig 5—The woman of figure 4, lying down. The bloating has suddenly disappeared.

when I doubled him up, it disappeared for good. One of the women whose case is described in this report had a similar "tumor" in the lower half of the left rectus muscle. In the case of another bloater, a man, the wife noted that at times there were "knots" in the right rectus muscle. In the case of 1 woman bloater, the anterior abdominal wall would suddenly become tense and then relax, and it is probably highly significant that in 3 other cases, with the bloating and the cramping of the abdominal muscles, the women had cramps also in the muscles of the arms and legs or of the thoracic wall. Seventy years ago, Mitchell⁵ saw bloaters with these "small phantom tumors" of the pectoral and other muscles. Talma,¹² in 1886, commented on one-sided bloating.

In 1 of my cases, the woman suffered for years from cramps in her thigh and abdominal muscles, so sudden and severe that they often threw her to the ground or caused her to fall downstairs. Such falls raised

the question of possible epilepsy, but she said that she never lost consciousness. At night, the spasms would cause a knee to jerk painfully up to her chin and would wake her, screaming. She said that when she was bloated, her arms and legs would stiffen.

In another case, the woman, when beginning to bloat, felt a sensation of spasm traveling up the esophagus to the throat. Another, during the spells, would have some trouble swallowing solid food, indicating spasm

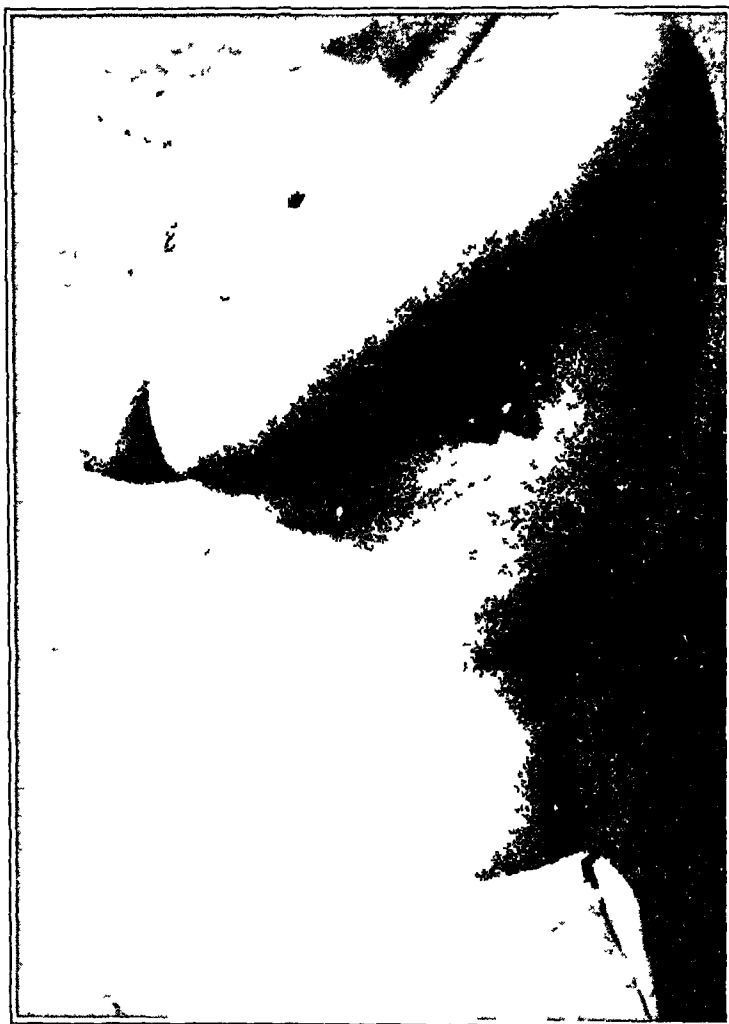


Fig 6—A bloater slumped into her usual posture

of the esophagus. Two other patients experienced painful cramping of the rectum or of the anal sphincter. In another case, just before bloating began, the patient would feel something snap or "block" in the right lower quadrant of the abdomen, the whole abdomen would then become so sore that it hurt her to walk. One woman said that at the beginning of a spell she felt as though a band were tightening in her epigastrium. Perhaps highly significant of a psychic cause for the phenomenon is the fact that 1 woman felt as if a hand were grasping the anterior abdominal wall and pulling it forward.

Osler²⁰ and a number of other writers on the subject of bloating noted the contractions of the rectus abdominis muscles. Haultain¹⁶ said that he saw sudden bloating in 2 cases of patients with an obviously relaxed abdominal wall, 1 was a man who had just been subjected to paracentesis and the other, a woman who had just had a large ovarian cyst removed. One coughed violently, and the other vomited, in each

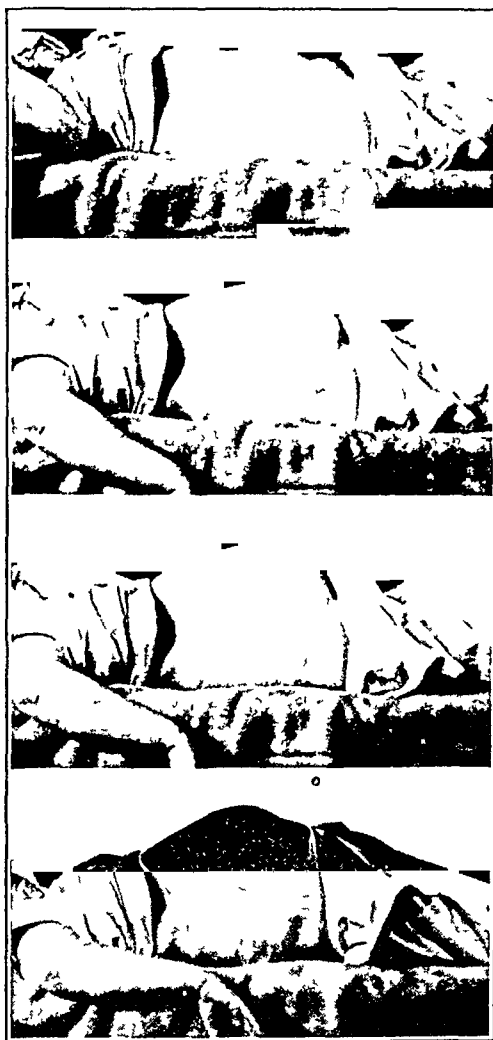


Fig 7—Several stages in the rapid bloating which took place when a woman's hand was placed in ice water. (From Vaughan²³)

case, with the accompanying spasms of the abdominal muscles, the patient bloated.

Some horses bloat in an effort to avoid having a saddle girth cinched tightly. They probably do this by contracting the abdominal muscles.

The Diaphragm—For a time I suspected that the bloating was due to a pronounced descent of the diaphragm, and in a few cases, while watching with the roentgenoscope, I saw this action taking place. The

diaphragm dropped to its lowest possible position, and its movements then became shallow and irregular. In other cases, however, the diaphragm was up in its normal position when observed. Contrary to the theory that a considerable descent of the diaphragm was the main cause of the bloating was the observation that no matter how deep a breath some patients might take, they could not produce the typical bloating. Interestingly, one woman's attacks of bloating began with

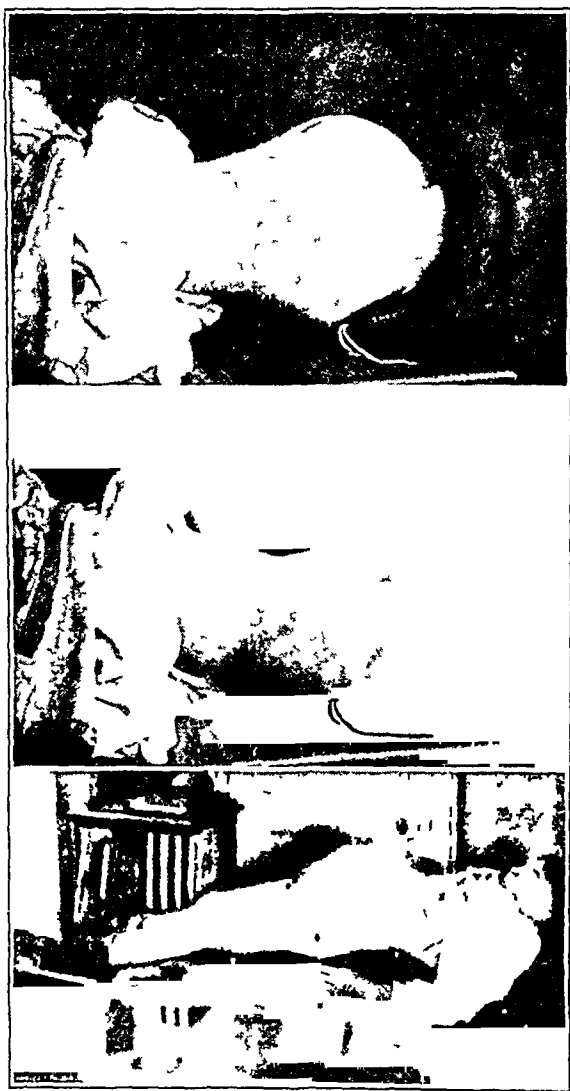


Fig 8—Top, a girl when bloated, center, the same girl after she had obeyed the command to deflate. Bottom, another bloater. (From Kaplan³)

hiccup and another's with sneezing, which suggested involvement of the diaphragm. Talma mentioned a bloater whose condition became worse when he was hiccuping. Kaplan's photographs show how, in some bloaters, the abdominal contents are pushed caudad (fig 8).

The fact that in a few cases the diaphragm, with its cervical innervation so far oral to that of the other abdominal muscles, joined in the spasm, indicated that the storm causing all the contractions was arising

in the brain One wonders whether, perhaps, spasms in the diaphragm, brought on by emotion, often caused the ancients to use the same word for the diaphragm as for the brain Some modern words, such as "frenzy" or "schizophrenia," have such an origin

Osler,²⁰ who knew bloaters, stated the belief that the distention must be due largely to spasm of the diaphragm, and a similar view was held by Talma,¹² Da Costa,¹⁴ Gowers,⁹ Kerr and Ferguson,¹⁷ and others Simpson⁴ said that he could sometimes make bloating disappear by relaxing a patient's diaphragm He did this by having the woman take a deep breath and then exhale, or by having her count aloud as long as she could without taking a breath

Several Mechanisms—As I have already admitted, in some cases, especially when there was no pronounced lordosis or no considerable flattening of the abdomen when the patient lay down, I was at a loss to explain the mechanism which produced the bloating As Kausch,²⁴ Fitz²⁵ and others said long ago, there must be several ways in which a neurotic woman can make her abdomen bulge forward I can only be certain that in most cases described in the present report, the bloating was not due to any increase in the bulk of the intestinal contents

Kaplan's photographs (fig 8) suggest that there is something in Schatz' contention (1872) that when much pressure is put on the contents of the abdomen, as on a balloon, it tends to assume a globular form

THE TYPE OF PERSON WHO BLOATS NERVOUSLY

In the present series of 92 cases, there were 85 women and 7 men This sex distribution alone indicates a functional origin for the disease, because organic diseases of the abdomen, with few exceptions, involve 3 or 4 men to 1 woman Eighteen of the women were unmarried (an abnormal proportion), and most of these were too psychopathic or undersexed ever to marry Few of them had ever gone out much with men, one said that she never wanted to go out with men, several had no sexual feeling, and one was a nun who was said by her Mother Superior to be "a bit difficult"

Seven of the women who had married had been divorced, and at least 22 of those who were still married were unhappy, or had made a poor sexual adjustment Four remarked that they had made a mistake in marrying a man too old for them, 1 had married a dipsomaniac One, who had married at 17, was still a virgin at 55! She said that her

24 Kausch, W Beitrage zur Hysterie in der Chirurgie, Mitt a d Grenzgeb d Med u Chir **17** 469, 1907

25 Fitz, R H The Relation of Idiopathic Dilatation of the Colon to Phantom Tumor, and the Appropriate Treatment of Suitable Cases of These Affections by Resection of the Sigmoid Flexure, Am J M Sc **118** 125, 1899

husband's few early attempts at intercourse had caused her so much pain and disgust that thereafter he had left her alone. She had a toxic goiter, and her 2 sisters, also goitrous, were queer "old maids."

The most frequent comment in my notes as to the personalities of the women bloaters was "very nervous." Many were described as "constitutionally inadequate" and always ailing, shy, with a negative or schizoid personality, or very sensitive and worrisome, tense, irritable, often tired, sometimes depressed, psychopathic, and inclined to cry without apparent cause. At least 16 were unstable and had had one or more nervous breakdowns or mild depressions. Two had been mildly manic at times, and 2 had attempted suicide. One had been in a psychopathic hospital. Three confessed to an almost insane temper, 3 had had spells of anorexia nervosa, 1 patient said that she was a "screwball", 3 had low intelligence, several were often jittery, excitable and shaky, several feared that they were going insane, others jerked and feared a convulsion, some had feelings of confusion, or of being drugged, and others had severe claustrophobia. Two said that they had had an unhappy childhood because of mean parents, and many were most unhappy and full of grief when I saw them. Two had much strain and sorrow because of mentally defective children.

Several patients tended to hyperventilate when nervous, others suffered from palpitation or spells of smothering, several fainted easily, 1 had facial tics, several got dizzy easily, and 1 salivated at times. Some had terrible nightmares, many fretted a great deal, 1 as a girl had been stricken with diarrhea whenever a beau came to visit her. Some said that they had pains all over their bodies, 1 was a chronic follower of quacks of all kinds, several had nerves that played tricks with them all the time, 1 suffered from neurodermatitis, some had air hunger at night, 1 had had chorea, some reacted adversely and violently to drugs, a sign of a nervous makeup. Evidently, most of these patients were anything but normal neurologically.

Menstruation—As is often the case with psychopathic women, at least 14 suffered from dysmenorrhea and some, from severe premenstrual tension. Seven mentioned a scanty flow. At least 2 mentioned flooding. For no detectable reason, 1 stopped menstruating at the age of 21, and several submitted early in life to hysterectomy. Several had a male distribution of body hair, suggesting poor ovarian function.

Appearance of the Patient—In spite of the high percentage of psychopathic and neurotic persons in the group, I noted comments, on the history sheets, indicating that 13 were pleasant persons and that several were lovely, attractive, well built women who looked well. Indicating neurosis was the fact that in spite of much suffering, at least 11 were overweight. Only a few were too thin.

Hysteria—Many of the women, while under observation, had hysterical episodes, with such symptoms as paralysis, aphonia, shuffling gait, locking jaws, queer, overemotional behavior or attacks of severe air hunger. A dozen others told of hysterical attacks, with "unconsciousness" lasting several hours. Five gave a history of illnesses which had been considered episodes of encephalitis, but which sounded to me more like prolonged attacks of major hysteria, none of the episodes had left any residue of parkinsonism. A few patients were reacting badly to a physical handicap, as in the case of a woman who was an achondroplastic dwarf and that of a man who was born without one ear and with only half the mandible.

Hypersensitiveness—Many patients were of the hypersensitive type, 1 said that whenever she was to start on a journey, she would lie awake all night and would urinate every fifteen minutes on the day of the trip. Several had an irritable bowel syndrome, with the formation of much mucus. Several patients, with a normal heart and thyroid gland, had a pulse rate between 120 and 140 beats per minute when first interviewed, later the rate became almost normal. Some had submitted to thyroidectomy without obtaining relief.

One woman was so hypersensitive that she could not stand a simple rectal examination. Most patients had greatly exaggerated deep reflexes. In 1, the knee jerk was so strong that the leg on the other side jumped too. When I touched a trigger zone on 1 woman's back she belched repeatedly.

Racial Stocks—No particular racial stock seemed to predominate in this group of patients.

Migraine—At least 32 of the 92 women suffered, or had suffered, from migraine. This incidence is higher than that in the clientele which I see usually and would suggest that some relation exists between the migraine and the bloating. Actually, all but 2 of the patients with migraine said that they could see no relation between the headaches and the bloating. In a few cases, the headaches had almost stopped before the bloating became a problem. In 1 case, however, many of the attacks suggested an equivalent in migraine.

The impression I gained was that the migraine only made the patients more sensitive and sickly, and therefore more inclined to bloat. Contrary to the idea that the present form of bloating is an equivalent of migraine is the fact that in 2 cases, the episodes continued during several pregnancies, in another case, however, the woman was free from bloating during pregnancy. Additional evidence against migraine as a cause of bloating was the fact that injections of ergotamine tartrate U S P (gynergen®) did not improve the condition.

REPORT OF CASES OF BLOATING IN MEN

Because there were so few men with the syndrome it is of interest to scrutinize their cases to see what sort of human beings they were

CASE 1—A painter of 45 was a sullen, nervous, intense man, much of whose history was typically that of a "relative of the epileptic" He was so irritable that he avoided arguments, for fear he might attack and kill his adversary He bloated suddenly when he became excited or angry, sometimes the distention woke him out of sleep He did not dare eat with friends, for fear he would bloat after taking a few mouthfuls of food, and he would not even permit his wife to be with him at table As was to be expected, his first wife had left him and his second was about ready to do so

When bloated he would salivate He would get up, walk around and rub his abdomen until he would belch explosively, thus obtaining some relief His tendency to bloat had appeared twenty years before, after a drinking bout Somewhat contrary to my theory that the patient was a "relative of the epileptic" were the lack of a family history of the disease and a fairly normal electroencephalogram Aside from the irritability and bloating the patient was strong and well

CASE 2—A worrisome clerk of 49 began to bloat when a physician sent him into a panic by telling him that he would have to have his appendix out With the bloating, severe globus hystericus occurred The patient appeared to be a typical bloater, with no flatus

CASE 3—A not-too-successful attorney of 36 had a deforming facial defect, which handicapped him and caused much mental suffering His bloating seemed to be typically nervous in type

CASE 4—A big, husky farmer of 61 appeared to bloat typically, relief occurred with a gurgle He had the usually neurotic "hurting" of one-half the body, from head to foot

CASE 5—A man of 47 had lifted himself by hard work from a job as a mechanic to that of service manager of a large corporation He had three phones clanging on his desk from 7 a m until midnight For ten years he had had spells in which he would get tense and then bloat A little whiskey would bring prompt relief In the spells, the right side of the abdomen became rigid The patient smoked three packages of cigarets a day He had a deformed duodenal cap, but no symptoms of ulcer

CASE 6—A small, depressed-looking, nervous, constitutionally inadequate stock clerk of 58 had typical bloating after eating, annoyance or exertion, such as that needed for mowing the lawn "Knots" developed in his rectus muscles, which were relieved by his doubling up or lying down He was mildly manic-depressive in temperament He had been bloating for twenty-seven years He complained also of smothering spells and hot flushes

CASE 7—A stocky, muscular, cheerful, middle-aged man, with poor nervous heredity and unhappiness in his home, bloated frequently Hypersensitivity of the abdominal autonomic nerves was indicated by the fact that urination brought abdominal cramps and a feeling that diarrhea was impending

SIGNS AND SYMPTOMS

Heredity—Doubtless highly significant is the fact that in 16 of the 92 cases, a history of insane ancestors was recorded In 9 more cases, there was a history of epilepsy in near relatives, in 2 cases, the women

had defective children. Thus in 30 per cent of the patients there was a strong suspicion of poor nervous heredity. It may be significant that 7 patients had relatives with diabetes, and that 3 had relatives with toxic goiter. One woman's mother bloated. Many relatives had migraine and were allergic.

Age Incidence—Most of the 92 patients were in their thirties and forties when first seen, 9 were in their twenties, and 11 in their fifties.

Onset of the Disease—In 3 cases, the disease had begun in childhood and in 1, after measles. In several, it had begun when the patient was 16 or 17 (perhaps with the excitement of graduation). In some cases, the bloating had appeared for the first time shortly after an early and unhappy marriage, while in others it had followed an operation, a miscarriage, the death of both parents in an accident, an attack of severe indigestion, an episode of vomiting or diarrhea, an unexplained fever, a period of overwork or a child's first epileptic convulsion. One woman had begun to bloat when her maid left her, 1, when a maid stole her mink coat, 1, when she discovered her husband's infidelity, 1, after her marriage to a dipsomaniac, 1, while helping in an election campaign, 1, when her mother committed suicide, and 1 when, at Christmas time, she overate and took a cathartic for relief.

Another patient, a temperamental young woman, married a dashing fellow, found that she had gonorrhea and divorced the man, then, still much in love, she arranged for remarriage, only to find, a few days later, that the man had eloped with another woman! After unhappy experiences with another man, the woman began to bloat. Another woman began to bloat when she too found that she had acquired gonorrhea from her husband. One woman dated her illness from the mental shock of discovering at 28 that a surgeon had tied her fallopian tubes at operation. She had experienced a few months of overcompensation with nymphomania and then had become sexually anesthetic and had begun to bloat. In several cases, the woman was in love with a married man who was not free to marry her.

Exciting Causes of Individual Attacks—Many of the bloaters knew that the attacks were likely to accompany any excitement, pleasant or unpleasant, any argument or fright, much standing or walking, hard horseback riding, or anything that produced fatigue. One woman said that she bloated whenever she "got to feeling ugly." One bloated when frightened about her boy's attacks of asthma, other patients bloated when they became angry, or when they were hurt in any way, mentally or physically. Some had most difficulty when distressed by hot weather, some, when worried or tired after a sleepless night. The very nervous wife of a doctor bloated whenever her husband was called out at night leaving her alone in the house. One woman bloated whenever she

fussed over her husband's coming late to supper and another, when her husband complained about her cooking. Another began to bloat when she tried to break away from a domineering sister.

Most patients had found that any large meal, particularly supper, was likely to produce the distention. As a corollary of this factor, many patients remained fairly well when they ate but little. Some found that they could safely plan to go out in the evening if they would eat nothing at all during the day. One, however, on one occasion fasted for three days and still was bloated.

In some cases, constipation was an exciting factor, but it was not the only or the essential one, as shown by the fact that often when the bowels were moving well or the colon was kept clean with enemas, the women still bloated. Some patients even said that they dreaded a bowel movement or the taking of an enema, which might act as a trigger mechanism and start the bloating. Some said that they would be well if only they could do without defecation. In 7 cases, enemas helped a bit in averting the spells, however, enemas rarely helped much during an episode, 1 woman took three a day and still remained bloated. Others took a daily cathartic and were the worse for it.

A few patients would experience bloating when they sat bent over forward. For that reason, 1 could not pick berries, and another could not sit hunched over in a boat, fishing.

Effects of Menstruation—Curiously, in the cases of the women, only 10 said that menstruation was a factor in bringing on attacks. In the cases of 2 of the more psychopathic women, the bloating was associated with premenstrual tension.

Time of Day—About equal numbers of the patients experienced bloating before daybreak (waking them), before breakfast, after breakfast, after supper and in the evening. Most of them said that the distention appeared during the afternoon, or within a few minutes after any large meal. Some said that the bloating might come at any time, others said that it never came in the early morning. Many said that they usually awoke feeling well in the morning.

Length of Episodes—The great majority of women said that the bloating almost always disappeared overnight. Eleven women said that an attack might last from two to four days, and a few others said it might last one or two weeks.

Condition of the Abdomen—In some cases, the patient's abdomen was as tense as a basketball, while in others, it was fairly soft. In the office, a woman might have a tense abdomen one minute, while the next minute it would be relaxed. Usually the percussion note was not unusually tympanic. Often the abdomen was not tender to the touch. In most cases, the patient did not seem ill.

Pain or Discomfort—Many women spoke of discomfort, misery, aching, distress, hurting, burning, gnawing or of a feeling of distention, pressure or bursting, when bloated. A few had pain so severe that they walked the floor groaning, grunting or grinding the teeth. A few behaved like a woman in labor, with pains coming every four or five minutes. Because of this suffering, at least 2 of the women became habituated to morphine and several were in danger of this. In most cases the pain was constant, but in a few it was rhythmic, 11 women spoke of cramps. A few thought that the pain arose in the contracted muscles of the abdominal wall. As one would expect, because of the forced lordosis, a few had backache during spells. In some cases, there was pain only during some years of the illness, or during certain attacks. One patient said that pain "ran up into the head." Only 2 mentioned soreness of the abdomen. Five said that they would get sore all over. Some were so sore that they liked, during spells, to lie on the side with the knees drawn up. When in a crowd, they were much afraid of being jostled.

Twenty patients said that they had little, if any, discomfort. These complained only of their appearance, which, especially in the case of an unmarried woman, was embarrassing. In some cases the woman was too ashamed to go out in public, and in a few her appearance interfered with her holding a beau. One said that her friends amused themselves by watching her bloat after a meal.

Location In 5 cases, the pain began or stayed in the upper half of the patient's abdomen, in 3 each, it was in the left half or the right lower quadrant. In 1 case, it was in the left lower quadrant. In 1 each, it was in the right upper quadrant, the lower half, the right half or all over the abdomen, up into the thorax. In the case of 1 woman, it often closely resembled the pain of gallstone colic, but cholecystectomy did not help.

Peristalsis—The pain, when present, did not appear to be arising in contractions of the bowel, because of the quietness of the abdomen. In only a few cases was there any borborygmus during a spell, and in only 1 case was there ever any visible peristalsis, this did not occur during bloating. Most patients said that while they were bloated they had no desire to move the bowels and never passed gas. Most of them could eat and digest while bloated, in only 2 cases was gastric stagnation noted. In these 2, roentgenologic study showed neither a pyloric lesion nor pyloric spasm to explain the stasis.

Terminal Gurgle—Interestingly, several patients stated that a few moments before the swelling receded they would hear a gurgle in the upper part of the abdomen or on the right side. One woman would hear this gurgle after taking morphine, which would stop the bloating.

Another woman, after hours of suffering, would say, "Here's the gurgle, it's going to let go," and in a few seconds she would be relieved. This feature suggests that some center in the nervous system not only causes the abdominal muscles to contract but also stops movements of the bowel. When the "storm" in the center lets up, the bowel apparently relaxes first, allowing a bubble of gas to move caudad. The terminal gurgle appeared in 1 case only after the taking of a big dose of atropine, perhaps with some morphine.

Some of the women noticed a large flow of urine at the end of an attack, such as is seen in some spells of migraine.

Other Symptoms—Twenty-five of the women complained of nausea, and in 6 cases, the symptom was severe. Seventeen vomited during certain spells. Three induced vomiting, in an effort to get relief. One had sudden, uncontrollable spells of projectile vomiting, even with an empty stomach. Some recovered from the vomiting with the passage of time. At least 15 were subject to attacks of belching, 3 of these were accomplished air swallows. Seven spoke of mucous colic and 3 of heartburn. Ten regurgitated food soon after eating, always a nervous habit. Seventeen had an occasional attack of diarrhea, almost always between spells. Several had a headache when the spell lasted a long time. At least 28 of the women were constipated. Five complained of dizziness, with or without bloating. Some got weak in the knees during spells and were unable to stand. Four patients commented on an occasional rather sudden loss of from 20 to 40 pounds (9 to 18 Kg.) in weight.

Other seldom mentioned symptoms were a feeling of interference with breathing, profuse sweating, a feeling of being dazed, quivering and the advent of bad breath. Only 1 stressed occasional fever.

ADDITIONAL FACTORS

Relation of the Disease to a Trigger in the Digestive Tract—It is important to note that most of the patients with this disease had an excellent or fair digestion, not only between the attacks, but even during them, in other words, the indication was that the bloating was not due to indigestion or to any lesion in the digestive tract. This agrees with the fact that in almost all cases, repeated roentgenologic studies and abdominal explorations had failed to show any significant lesion. In the 3 cases in which the gallbladder was probably diseased and was removed, the bloating returned sooner or later, unchanged. In a few cases, the disease actually began after the removal of the gallbladder or the appendix. In all but 10 cases, the person was unusually free from abdominal gas and from the need for passing flatus, only 4 occasionally got some relief by passing gas.

The fact that a number of patients would bloat as soon as they started chewing one mouthful of food, or after drinking a glass of cold water, taking an enema or defecating, suggested strongly that the digestive tract contained triggers that could, in a purely mechanical way, start a train of reflexes. The condition may be like that in *tabes dorsalis*, in which, as Foerster²⁶ once pointed out, eating can serve as a trigger to start a gastric crisis.

Allergy—Allergic sensitiveness appeared to aggravate the situation in at least 25 cases. In 14 cases, the patient was sure that the nature of the food eaten had no effect on the bloating. In many, an elimination diet did no good. In only 4 was it decidedly helpful, 2 women said that they could stay well as long as they ate only meat or cottage cheese. Four patients were asthmatic, 2 had hay fever and 3 had urticaria. Others showed no sign or symptom of allergy.

The suddenness with which most patients bloated after a meal was evidence against an allergic mechanism. There was hardly time for it to act.

Coexistent Conditions—A few patients had conditions or histories which were probably only coincidental, because they were not present in the other cases. I refer to mild hypertension in 7 cases, paroxysmal tachycardia in 2, extrasystole in 2, a primary type of anemia in 2, the resection of a segment of bowel in childhood in 2, pruritus vulvae in 2, a scar of an old duodenal ulcer in 2 and a pseudoulcer type of syndrome in 4. A few had a small, nontoxic adenoma of the thyroid gland. Several had no free hydrochloric acid in the stomach.

Negative Results of Examinations—In the present paper, space is not given to reports of the careful medical examinations made because, in every case, they failed to yield any positive or significant findings. The blood pressure was almost always normal. In all cases, the patient's stomach, gallbladder and colon had previously been well studied roentgenologically, the organs were usually studied again at the Mayo Clinic, with negative results. In a few cases, the small bowel was carefully studied roentgenologically and was shown to be free of any obstruction. In several cases, the function of the liver was studied, and no retention of dye was found. In some cases neurologic studies were made, which showed nothing significant. In the few cases in which the spinal fluid was examined, it was normal. Electroencephalograms were essentially normal in 3 cases and showed dysrhythmia in 2, in these 2 cases, the bloating may have been an epilepsy equivalent. As already noted, in most cases the patient's

26 Foerster, O. *Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Sonderbande zu Bruns' Beiträgen zur klinischen Chirurgie*, Berlin, Urban & Schwarzenberg, 1927.

abdominal cavity had been explored repeatedly, with essentially negative findings

Efforts to Avoid Bloating—No good method has been found for avoiding the attacks. Some women had fewer spells when they avoided fatigue, exercise, annoyance, conflict, loss of temper and overeating. Four were almost well when they stopped working and took a rest. Four were much better when they stayed in bed. Two were all right if they lived on meat or cottage cheese, and 17 were much better if they ate very little. Four were helped by wearing a tight girdle. One could prevent an attack by taking an injection of estrone U S P (theelin®), however, I tried this treatment on a few women, and only 2 obtained even slight benefit. Two said they could avoid attacks by taking laxatives, and 7 were somewhat better for the taking of enemas. On the other hand, 1 woman said that she could avoid attacks by restraining defecation for days.

Some of the women might have recovered if they could have got rid of a bad husband and found a good one. Some might have been cured by a good annuity. Others might have been helped by a psychiatrist. In a few cases, an elimination diet helped. A few women could have helped themselves by reducing weight. They would have had a much smaller abdomen.

In most cases, bromides and barbiturates had been tried without avail. Krukenberg's patient was helped by wearing a back brace, which combated the tendency to lordosis.

Uselessness of Operations—As already noted, most of the women had been operated on many times, with no permanent relief. Happily, some twenty years ago we at the Mayo Clinic learned never even to explore the abdomen of these patients.

Following is a list of the operations submitted to by 1 woman between 1929 and 1941: Appendectomy, abdominal exploration, removal of an ovarian cyst, cholecystectomy, removal of adhesions, thyroidectomy, removal of a big toe, resection of a segment of the small bowel, removal of the coccyx, curettage and left mastectomy. Another woman had, in succession, appendectomy, suspension of the uterus, removal of an ovary, lumbar sympathectomy, cholecystectomy and removal of adhesions. One had, in nine years, salpingectomy, right ovariectomy, left ovariectomy, drainage for postoperative peritonitis, removal of adhesions and suturing of the right kidney; in one period of fourteen months, she was hospitalized five times. These are not unusual records for bloaters. As will be noted, some of these women get themselves operated on not only for bloating but for other troubles, such as a sore coccyx. This practice throws light on their temperament.

The point to be noted by all surgeons is that every one of the operations performed in these 92 cases with the hope of curing the bloating was without result. Even in the few cases in which gallstones

were found and removed, the bloating went on as before. The reason for this 100 per cent failure of surgical intervention would appear to be that in this disease the cause is never in the abdomen.

Another important point for the surgeon to remember is that if on anesthetizing a bloater in an acute attack the abdomen should become flat, the proposed operation should be called off, the diagnosis of functional bloating will have become obvious. The importance of this observation was stressed by McDonnell¹³ as long ago as 1855.

As yet, even some eminent surgeons do not recognize this disease and do not know the futility of operating in an attempt to find the cause of it. At the time of writing, 1 of the highly neurotic women whose case is reported here has just had her sixth operation at the hands of one of America's leading surgeons. Since her basic trouble is that she married an old man whom she hates to live with, she is still bloating.

Efforts to Terminate Bloating—The treatment of attacks is unsatisfactory. At least 17 of the patients said that the only way to obtain relief was to lie down and rest. Three said that they could get some relief by violent belching, 2, by washing out the stomach, and 2, by eating some food.

At least 9 knew that an injection of morphine, dihydromorphinone hydrochloride U S P (dilauid hydrochloride®), meperidine hydrochloride (demerol hydrochloride®) or codeine would relieve them. All that saved some from habituation was the fact that morphine made them very ill. One continued to bloat even when she was taking 1½ grains (0.1 Gm) of morphine each day, the drug only lessened her pain. A few patients were not helped much by morphine. The abdomen would not become flat when it was used. One woman was helped by an injection of posterior pituitary injection U S P (pituitrin®) which made her bowels move, but the case was atypical. Another woman tried the same drug without avail. Many other drugs, such as epinephrine, belladonna extract, atropine, benzyl benzoate, alcohol, amyl nitrite and histamine phosphate, were tried repeatedly without result. One man got good relief with whiskey, but a woman who tried it only became more nauseated. One woman could get prompt relief from an intravenous injection of pentobarbital sodium U S P, but in several cases, barbiturates only made the patient "wild." Only 1 woman said that she got some help from injections of gynergen®. In my hands, gynergen® and dihydroergotamine tartrate (DHE 45®) did not help bloaters. One patient got some help from neostigmine methylsulfate U S P. In bad attacks with much vomiting, a 3 grain (0.2 Gm) rectal suppository of pentobarbital sodium U S P or an intramuscular injection of 3 or 7½ grains (0.2 or 0.45 Gm) of amobarbital (amytal®) sometimes helped. Two patients would take some bicarbonate of soda and belch. In some cases enemas helped to calm

an attack, but in most cases they were of no help, in 3 cases, they made matters worse

In Goldschmidt's case,⁶ splanchnic anesthesia did not help, and the administration of epinephrine made the girl worse. Her abdomen would become flat after an injection of ergotamine tartrate or afenil® (a molecular compound of calcium chloride and urea), but soon she would bloat again. In the case reported by Bargen, Adson, Lundy and Dixon,²¹ splanchnic block caused the bloating to disappear. It is said that Janet could sometimes stop an attack by "suggestion." Kaplan said that his teacher, Bernheim, could make a bloated woman's abdomen become flat by ordering her to stop bloating. Several early writers told of stopping an attack by exerting steady manual pressure on the distended abdomen.

USUAL COURSE OF THE DISEASE

Because I saw most patients in consultation and then seldom heard from them again, I cannot say much about their subsequent histories. Only 1 of the women lived near enough so that I could observe her progress through the years. She largely recovered from the bloating when she adjusted fairly well to an unhappy domestic situation, but at the time of this report she still has one nervous trouble after another.

Another woman stopped bloating but is still a nervous complainer. Highly informative is the fact that a woman who had bloated severely, and who had been incapacitated by this disease for half a lifetime, recovered when her dipsomaniac husband died, since his death she has been happily at work in a store. Another patient, seen after an interval of ten years, was still bloating, others had had several more operations and had been hospitalized several times for morphinism. A few others reported after some years that they were better, but still bloating occasionally. That the disease is often long lasting and fairly hopeless can be seen from the fact that when I first saw some patients, the condition had been recurrent for ten, twenty or thirty years.

In the worst cases, and especially when there is a large element of psychopathy, with low intelligence, or a bad domestic situation with constant strain, unhappiness and frustration, the prognosis is bad, and I know of nothing likely to help. The woman continues to go from one clinic or physician to another, wasting large amounts of medical time and often large amounts of the charity funds available in her city.

Unfortunately, most of the women I have heard from were having more useless operations. One wrote me that after the usual series of appendectomy, cholecystectomy, partial hysterectomy and operations for adhesions, she had had lumbar sympathectomy, left phrenicotomy and bilateral splanchnicectomy. The appearance of her abdomen years ago, when I first knew her, is shown in figure 9. When last I heard

from her she was no better, though she thought that the sympathectomy might have stopped the vomiting during bloating. Her real trouble, I think, was that she was in love with a married man. Another woman reported that an abdominal sympathectomy had failed to give relief.

One woman returned years after examination to say that she had been cured miraculously by a chiropodist, who had placed a pad under the anterior end of her os calcis to tip it up!

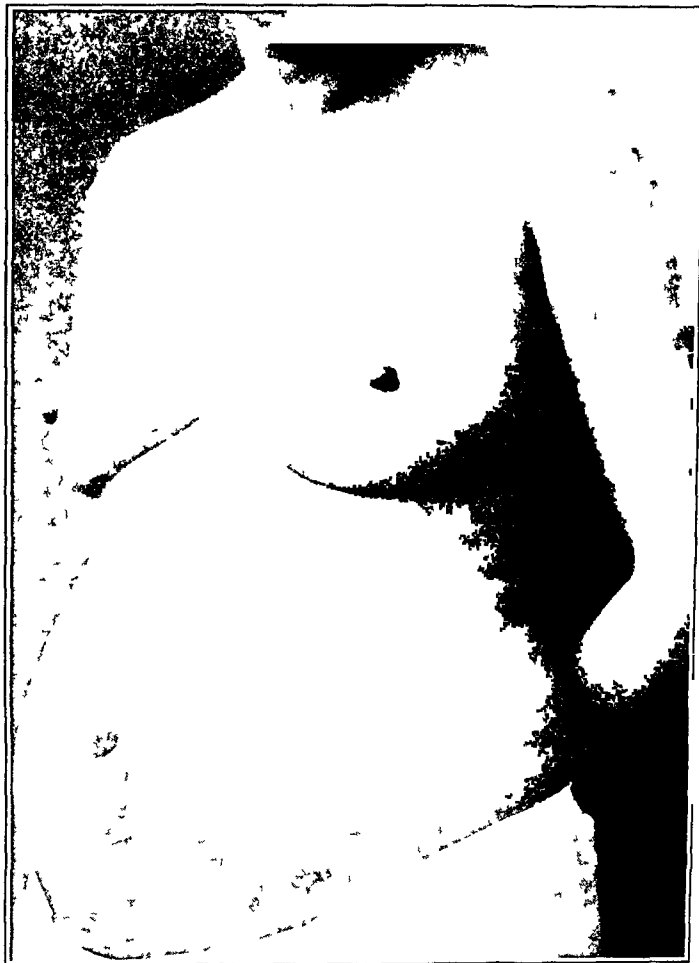


Fig 9—Typical scarred abdomen of a bad bloater

EARLY STUDIES OF THIS AND RELATED DISEASES

The earliest report I found of a phantom tumor in a hysterical girl was that by Bright²⁷. Even in the preanesthetic and preaseptic days of 1824, this girl had already had two futile abdominal explorations when Bright saw her!

²⁷ Bright, R. Hysterical Distention of the Bowels, Mistaken for Ovarian Tumor. Operation to Attempt Its Removal, *Guy's Hosp Rep* 3 257, 1838

O'Donnell, in 1855, and Priestley, in 1858, showed that by giving chloroform one could diagnose hysterical bloating. In 1871, Cadet described a case of hysterical bloating in which the spell lasted several days. Kaplan stated that in 1872, Wells described and pictured cases of nervous bloating.

In 1881, Mitchell described a patient with nervous bloating whom he had seen some twenty years before. The patient was a woman whose life had been embittered by marriage to a worthless man. After losing all her money, she began to have spells of pronounced enlargement of the abdomen, due not to flatulence but to painful emotion. Mitchell learned years later that she had gradually got well. He saw another patient in whom any handling of the anterior abdominal wall would cause the muscles to contract, producing a phantom tumor.²⁸

Krukenberg's description of the disease, made in 1884, is good, and Kaplan's thesis on the subject, published in 1900, is excellent; he briefly reported 18 typical cases, collected mainly from the literature. Kaplan, and later Kausch, gave a good introduction to the older literature on the subject of the hysterical abdomen. Kaplan stated that in some cases, the diaphragm descended considerably, in 1, the bloating was on only one side.

Zeckendorf,²⁹ in 1883, reported what were probably 2 typical cases, but he did not understand the problem so well as Kaplan.

In 1922, Goldschmidt⁶ described a typical case of severe, painless bloating, the patient having a tense abdominal wall and no gas. A woman of 22, who was at times hysterical, was operated on four times in one year for what was thought to be intestinal obstruction. Each time the surgeons could find only an empty, contracted bowel. As soon as she left Goldschmidt's care she had another laparotomy, she continued to bloat for years.

In 1931, Christianson and Borgen¹ reported 5 cases of nervous bloating associated with obstipation and pseudoileus, and in 1936, Borgen, Adson, Lundy and Dixon²¹ described the case of a hysterical woman who was a bad bloater. Their picture of her (fig 3) shows the pronounced lordosis and the way in which it pushed the abdomen forward. She maintained the lordosis even when lying down.

In 1945, I reported 2 curious cases,²² 1 of severe bloating evidently due to spasm of the abdominal muscles, and the other apparently of hysterical contraction of the abdominal muscles without bloating. In the latter case, the powerful contraction of the muscles in the anterior abdominal wall kept the abdomen flat.

²⁸ Mitchell, S. W., cited by McArdle and Kolipinski.¹⁰

²⁹ Zeckendorf, E. Ueber die Pathogenese der Bauch tympanie, nebst Beiträgen zur Lehre vom Stoffwechsel bei der Hysterie, Göttingen, L. Hofer, 1883.

McArdle and Kolipinski,¹⁰ in 1886, Paddock,³⁰ in 1928 and Bivin and Klinger,³¹ in 1937, summarized most of the literature on spurious pregnancy and phantom tumors

According to Bivin and Klinger,³¹ who collected reports of 427 cases of phantom pregnancy, Hippocrates reported 12 of them, but I have not been able to find the reference. This syndrome of pseudocyesis appears to be a variant of the bloating disease described in the present paper. In pseudocyesis, the woman thinks herself pregnant and may remain bloated for months. She may have morning nausea, amenorrhea, breast changes and what she thinks is quickening, and she may even appear to go into labor. Bodenheimer³² reported the case of 1 of these women, who on several occasions was rushed to a hospital because she thought she was in labor. She finally became so well known to the admitting surgeon that he would send her home without even examining her!

SUMMARY

A syndrome is described, consisting of pronounced bloating, due not to gas, but to a contraction of the abdominal muscles and often to the assumption of a lordotic posture, which forces the abdomen forward. Commonly the swelling increases gradually during the afternoon and decreases at night, without the passage of gas. Occasionally the swelling appears so fast, or disappears so fast without the passage of flatus, that it is obvious that there could have been no change in the volume of the abdominal contents. Roentgenograms made of the bloated abdomen never show any excess of gas, and exploratory operations never reveal any physical cause for the syndrome. Even when diseased organs or a few adhesions are found, their removal does not produce a cure.

Ninety-two cases are reported, 85 of the patients being women and 7 men. Almost all were nervous, unhappy, neurotic or psychopathic. Many were relatives of insane persons or of those with epilepsy, migraine or diabetes. Most patients had good digestion between spells and sometimes even while bloated.

In these cases, the abdomen became flat a few seconds or minutes after (1) the induction of spinal or general anesthesia, (2) the blocking of the splanchnic nerves with procaine hydrochloride U S P, (3) the onset of vomiting, (4) the reception of an injection of morphine, or (5) the doubling up of the patient so as to alleviate the lordosis.

30 Paddock, R. Spurious Pregnancy, *Am J Obst & Gynec* **16** 845, 1928

31 Bivin, G. D., and Klinger, M. P. Pseudocyesis, Bloomington, Ind., The Principia Press, 1937

32 Bodenheimer, J. M. Pseudocyesis, *New Orleans M & S J* **81** 632, 1929

Often the bloating appeared again as soon as the effect of a drug wore off, or as soon as the patient stood up and slumped

Most patients lost much or all of the bloated appearances when they lay down, especially if the thighs were flexed on the abdomen

In some cases, only part of the abdomen bloated, and only parts of the abdominal musculature became contracted. The diaphragm was sometimes involved

The mechanism of the attacks appeared to vary somewhat in different patients, as did the symptoms. Some persons had pain, and others did not

The nervous "storm" which produced the contraction of the abdominal muscles appeared to quiet the bowel, and in some cases, the attack terminated shortly after a gurgle was heard in the abdomen

In many cases, an overly irritable digestive tract appeared to serve as a trigger zone, from which the bloating could be started. In such cases, a drink of water, defecation or the taking of an enema could start a spell

Bloating often began after excitement, annoyance, fright or fatigue. Large meals also tended to cause bloating, some women could avoid it by going without food all day

Physical, roentgenologic and laboratory examinations failed to show anything contributory

No effective, safe way was found to terminate the attacks. Morphine will sometimes stop distress and flatten the abdomen, but the danger of using the drug is great, 2 of the patients became addicts. A suppository of pentobarbital sodium U S P or an intramuscular injection of amobarbital sodium (amytal sodium®) may quiet the symptoms.

The prognosis for recovery is poor, but some patients recover when life becomes easier or happier

No exploratory operation should be performed. If one is proposed during an acute attack and the swelling goes down during anesthetization, the diagnosis of functional bloating is made, and the operation should not be performed

A review of the literature shows that nervous bloating has been observed for over a hundred years

MEDICAL ASPECTS OF SUBMARINE WARFARE

The Human Factor As Reflected in War Patrol Reports

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ALTHOUGH World War II produced a tremendous volume of literature on many phases of military medicine, little information is available in the unclassified literature concerning the medical problems of submarine warfare. It is my purpose, in this paper, to discuss the problems in the light of personal experience and of material available in reports of submarine combat patrols.

During the war, American submarines made over fifteen hundred patrols. The commanding officers' reports of fourteen hundred and seventy-one patrols were available for study to evaluate the human factor in problems of combat. The conditions under which the reports were composed and the insignificance of medical details as compared with data relating more specifically to the mission of the submarines account for some inadequacies of this source of information. Commanding officers were not trained medical observers, and the emphasis which they placed on the human factor in combat depended largely on personal aptitudes and interests.

The fourteen hundred and seventy-one reports on which this paper is based cover patrols made from Dec 7, 1941 to Aug 14, 1945. The great preponderance of patrols were made in the Pacific theater, from Australian to Japanese and Arctic waters. The majority were carried out by the modern "fleet type" submarines, a relatively small number of patrols were made by the smaller and obsolete "S boats."

To understand the conditions under which submarine officers and men lived and fought, a description of conditions aboard the typical submarine on combat patrol is necessary. It was an existence characterized by extremely crowded living and sleeping conditions, limited

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water supply, frequent high temperatures emanating from the engine rooms and humidity resulting from the shutting down of ventilation during periods of contact with the enemy. Many missions were marked by days of fruitless patrolling and of almost unbearable monotony and boredom, sometimes broken by contact with the enemy, when excitement and tension were at a high pitch. Some patrols, though of short duration, were extremely active, the men remaining at battle stations for hours on end.

It is common knowledge that submarines are built compactly and that living arrangements are dictated by, and secondary to, military requirements. Sleeping accommodations were so limited that with an average-sized crew of about 75 it was always necessary for some of the men to share bunks by sleeping in shifts. Stowage space for personal gear was extremely limited. The only recreations possible were reading, card playing and listening to records. Once the submarine was under way, no one was allowed topside except the authorized watch. An active patrol often necessitated dawn to dusk submergence, with the result that men did not see the sun for days at a time. While the ship was submerged, air within was cooled, freshened and recirculated by the air-conditioning units. Depletion of oxygen and accumulation of excess carbon dioxide sometimes occurred during periods of prolonged submergence. Though the supply of fresh water taken on at the start of the patrol was augmented by distillation, the total amount available was so small that showers frequently had to be limited. Condensate from the air-conditioning system was available for general cleaning, for use in the washing machine and sometimes for bathing.

Submarines had the deserved reputation of serving the best food in the Navy. However, the supply of fresh meat, vegetables and frozen foods was normally exhausted before the patrol was concluded, resulting in a monotonous diet the last few weeks.

The men and officers serving aboard submarines were carefully selected on the basis of high physical and psychologic requirements. Though a policy of frequent rotation to duty ashore was maintained, some men and officers accumulated an amazing number of war patrols on their record.

No physicians were assigned to duty on submarines in World War II, their place being taken by carefully selected and trained pharmacist's mates, of whose performance records the Navy is justly proud. Medical facilities and supplies, although not elaborate, were generally adequate and included sulfonamide drugs and, later, penicillin.

MILITARY SIGNIFICANCE OF HEALTH OF PERSONNEL

Exclusive of those lost on fifty-two overdue submarines, only 62 men died on operations, the causes of death appear in table 1.

The success of a submarine's mission was sometimes compromised by defects in the health of personnel or by defects in the habitability of the ship. Serious or widespread illness was reason for either termination or interruption of approximately 4 per cent of all patrols. The causes of termination of 29 patrols on the basis of illness are listed in table 2.

Personnel fatigue of this magnitude occurred only in the first two years of the war, terminating patrols of eight fleet type submarines. In five other instances, personnel endurance was exhausted and would have

TABLE 1—*Deaths Occurring Aboard Submarines on War Patrol*

Cause	Number of Men	Number of Patrols
Asphyxiation	26	1
Drowning (lost over the side)	17	13
Battle injuries	12	10
Accidents	3	3
Suicide	1	1
Pneumonia	1	1
Malignant lesion	1	1
Unknown	1	1
Totals	62	31

TABLE 2—*Conditions of Health Limiting Duration of Submarine Operations*

Condition	Number of Patrols
Excessive personnel fatigue	9
Illness of commanding officer	6
Battle casualties	5
Acute appendicitis	2
Multiple asphyxiations	1
Serious injury	1
Pneumonia	1
Mumps	1
Mental disease	1
Copper sulfate poisoning	1
Unknown (fever)	1
Total	29

terminated the cruise had not operation orders done so. There was nothing unusual about the illness of commanding officers. The remainder of these patrols were terminated consequent to unavoidable hazards and circumstances.

On approximately 2 per cent of all operations, unfavorable habitability became a major factor. On twenty-three patrols, reduced efficiency of operations was caused by or related to impaired habitability. Eight patrols were terminated due to deficiency of environment, the nature of which is listed in table 3.

Ships manned by tired and ill men were not effective fighting units. Illness, when it deprived the submarine of the services of key men, had considerable military significance. The impersonal and abstract qualities of figures make it difficult to convey the immediate importance of these data. However, the actual or threatened impairment of military potentialities which sometimes occurred is apparent in these selected excerpts from war patrol reports.

(On the fourth patrol of the N [1943])

Air-conditioning installations proved inadequate. The highest temperature and humidity level recorded was 124 F (51.1 C) and 98 per cent, during an invasion period lasting for about thirteen hours. Excessive heat and humidity reduced the efficiency of all hands to a considerable degree after about two weeks of operation.

TABLE 3—*Factors of Habitability Limiting Duration of Submarine Operations, Military Significance of Submarine Habitability*

Factor	Number of Submarines	Year
Lack of air conditioning	1	1942
Limitation of potable water capacity	4	1942 to 1944
Serious fire (battery)	1	1942
Serious fire (control room)	1	1942
Excessive copper sulfate content of drinking water	1	1944

The P on her fifth patrol had an experience sometimes encountered in northern operations.

The first dive made lasted longer than expected, with no carbon dioxide absorbent spread. At the end of fourteen hours all hands had difficulty in breathing, carbon dioxide concentration at that time being 2.5 per cent. 800 pounds of oxygen were bled into the boat, bringing slight relief. When the ship surfaced, two hours later, the concentration of carbon dioxide in the conning tower was 3.5 per cent.

The S was forced to submerge on one occasion on her seventh patrol, an enemy plane having been sighted. While she was still going down, a bomb or depth charge landed on her port side.

A terrific explosion jarred the boat. All hands not holding on to something were knocked from their feet. Fire started in the maneuvering room. All power was lost. Thick, toxic smoke filled the maneuvering and after torpedo rooms. All hands aft were sick. We went up and down three times and had started down the fourth time before power was regained. In the maneuvering room the situation was bad. All hands were violently ill. The angles which the boat had taken had not helped.

(On the second patrol of the P)

During operations the Commanding Officer collapsed partially and lost the use of his legs, apparently owing to an injury to the spine or the nervous system. This unfortunate illness necessitated return of the submarine to Saipan.

Mass illness cannot help but adversely affect performance aboard a submarine, as aboard the H

Loss of depth control on one attack was most unfortunate in that it prevented firing at a carrier. The order to make ready the tubes had been given rather late. This difficulty was combined with personnel errors in hurriedly preparing all tubes at this time nearly all the crew were handicapped by sickness from food poisoning.

The commanding officer of the S observed, with regard to illness of personnel

Decrease in the number of men in a crew on a long patrol does not permit flexibility of the organization without loss of efficiency when, through illness or accident, a man is placed on the binnacle list.

MEDICAL PROBLEMS

Infections of the Respiratory Tract—A high incidence of "colds" was commonly experienced within the first three weeks of the cruise, frequently before the submarine reached the operational area. These infections of the upper respiratory tract were sometimes associated with noticeable reduction of personnel efficiency. Patrols in northern operational areas, particularly in the winter, were occasionally handicapped by illness due, in part, to foul weather, the cold and dampness of the interior of the ships, overcrowding and inadequate protective clothing. Colds commonly accompanied the rapid passage from warm to cooler operational areas. The most practical form of prophylaxis was afforded by optimal atmospheric and living conditions while on patrol and by carefully supervised recuperation at rest centers. The effectiveness of germicidal lamps aboard submarines warrants investigation.

Injuries—The bridge of a submarine offers little protection, men were frequently seriously hurt in heavy weather. Because of the danger of being swept over the side in heavy seas, members of the bridge watch and gun crews and men working topside should be required to wear life jackets, whistles and man lights. The majority of injuries were unavoidable and were incurred while precipitously clearing the bridge or descending through the narrow hatchway. Accidental shifting of skids of torpedo racks in rough seas resulted in two serious head injuries, one of which was fatal. Poorly illuminated hatches accounted for many injuries. In gun attacks approximately 61 men were injured, 12 fatally. Explosions of ammunition seriously injured 8 men.

Diseases of the Gastrointestinal Tract—Appendicitis caused more anxiety than any other disease, the diagnosis was commonly made by pharmacist's mates. Although the illness interrupted or terminated patrols in 11 instances, not a single death is known to have followed appendicitis originating on a war patrol.

Psychiatric Casualties —A collection was made of the reports of cases in which disorders could possibly have been neuropsychiatric or emotional in origin. Apparently only those reactions interfering with performance of duty were recorded, for but 56 cases were reported. Statistically, this is an amazingly low incidence of emotional disturbances. In spite of the great responsibilities of commanding officers, there is evidence in the patrol reports of only 4 instances in which a crew lost confidence in their commanding officer or he lost faith in himself. It appears that the "breaking point" was indefinitely deferred and that psychiatric casualties were largely eliminated under conditions which submarines encountered in World War II. The reasons for this are important and have been classified elsewhere¹ in this manner:

- 1 Initial meticulous selection of personnel
- 2 Thorough and specialized training of personnel
- 3 High morale, associated with success of combat patrols
- 4 *Esprit de corps* among submarine crewmen
- 5 Adequate facilities for rest and rehabilitation and policies of frequent rotation
- 6 Frequent prepatrol and postpatrol medical examinations

AIR-SEA RESCUE OPERATIONS

Submarines recovered 549 survivors in air-sea rescue operations. The part played by the pharmacist's mates in this undertaking was very important. Forty-eight per cent of the aviators required medical care when recovered from the sea, although 18 per cent were seriously injured, only 2 died aboard submarines.

Submarines assigned to air-sea rescue operations should be especially prepared and equipped to permit increased bunking space and clothing allotments for survivors. Members of the rescue crew must be carefully picked and trained. Pharmacist's mates should be specifically indoctrinated as to the type and treatment of casualties expected.

FACTORS AFFECTING SUBMARINE HABITABILITY

Those conditions most frequently mentioned as influencing habitability were the inadequacies of ventilation and air conditioning, the discomforts incident to long dives (such as accumulation of carbon dioxide, depletion of oxygen, and increase of pressure and humidity), the weather, overcrowding, deficiencies of the water supply and sanitary tanks, fires, certain noxious agents, such as chlorine gas or carbon tetrachloride, and material damage consequent to depth charging or accidental flooding.

¹ Duff, I. F., and Shilling, C. W., *Psychiatric Casualties in Submarine Warfare*, Am J Psychiat 8: 607-613 (March) 1947.

Space permits discussion of only the more important components of habitability aboard submarines. In patrol reports, reference was made to habitability as indicated in table 4.

The figures in the table indicate the improvement in habitability which took place as the war progressed. After 1942, the percentage of "excellent" reports was doubled, the percentage of "fair" reports was significantly lowered and the percentage of "poor" reports was cut to one third. Reports of good habitability rose, to remain at a level between 55 and 60 per cent. It may be said, then, that about 70 per cent of all patrols reporting on habitability were made under either good or excellent living conditions.

A relation between reports of poor habitability and success of operations exists, although it is not constant. Thirty-nine of the sixty-three patrols experiencing poor habitability were successful, the majority of those that were not were made in the early years of the war.

TABLE 4—*Habitability Reports of Fleet Type Submarines*

Rating	1941		1942		1943		1944		1945		Totals	
	No	%	No	%	No	%	No	%	No	%	No	%
Excellent	0	0	8	8	24	16	41	14	33	16.5	106	14
Good	5	50	34	34	52	55	170	59	117	58.5	408	54
Fair	3	30	33	33	36	24	55	19	44	22.0	171	24
Poor	2	20	25	25	7	5	23	8	6	3.0	63	8
Totals	10		100		149		289		200		748	

Ventilation and Air Conditioning in Relation to Atmospheric Conditions—Contrary to popular belief, atmospheric conditions within a submarine submerging for a relatively short time are normal. Inasmuch as the hatches are closed before diving, the pressure within the boat is theoretically unchanged, actually, there is a slight rise in pressure, due to such factors as compression of the hull and leaking air tanks. When the ship is surfaced, a current of air is constantly sucked through the main induction valve (located in the superstructure of the ship) to the Diesel engines, and the engines exhaust the air from within the ship, setting up a current of fresh air through the open hatchways. When the ship is submerged, there being no means by which air may be obtained from the outside for combustion, the Diesel engines are shut down. The air contained within the ship is forcibly recirculated after passing through two main and one auxiliary air-conditioning units.

Without adequate air cooling and ventilation, habitability on an active war patrol may become so poor that material defects and decreased personnel endurance may compromise the effectiveness of the ship.

The relation of excess heat and humidity in the conning tower to the efficiency of control parties during long approaches to an enemy target is vital

To elude antisubmarine activity most submarines at one time or another "ran silent"² In only one patrol report was habitability, under such circumstances, reported as "good" Poor atmospheric conditions, the product of excessive heat, humidity, pressure, oxygen depletion and carbon dioxide accumulation, were the rule The manner in which the extremes of these conditions were tolerated by the carefully selected, trained and disciplined men was extremely important in determining whether a submarine would survive

With so many sources of heat, the temperature and humidity jumped to high levels in "silent running," particularly in the maneuvering room, where it sometimes reached 125 F (51.7 C) All hands stripped down to shorts, socks and shoes were removed, despite which men perspired excessively until, in an hour or so, the decks might be slippery with sweat Towels used to keep perspiration out of the eyes became wringing wet, shoes and socks could be wrung out like rags Every one drank a great deal more water than usual and took salt and aspirin tablets As time went by, the air became oppressive and stifling, and it was difficult to breathe, headaches were prevalent and severe It was often impossible to sleep, heat rash sometimes caused serious discomfort The enervation from the heat sometimes became so pronounced that physical exertion, such as that required to change or maintain depth, would exhaust the planesman Controllermen had to be spelled frequently Efficiency and reaction times were sometimes reduced considerably, errors were prevalent, even among key men There was a sharp increase in accidents when the damage of depth charging necessitated long hours of repair work Constant attention was necessary to see that instructions were carried out properly and promptly Tempers were short, nerves on edge The apathy which occasionally developed was startling

In one extreme case it was reported

As the youngsters folded up, the older and more phlegmatic men would take over Some without permission, others after requesting relief, would quietly leave their stations and lie down on the coolest spots of decking Occasionally stations ended up with two men taking turns, the off-watch man resting on the deck beside his station There was no evidence of hysteria, the men carrying out their duties to the limit of physical and mental endurance

Oftentimes on surfacing there were distressing nausea and vomiting Under such conditions the ship was no longer in a position to fight or

2 In "silent running," all men except those controlling the ship remained in their bunks, those who had to move about removed their shoes Talking was kept at a minimum, and all unnecessary noise, including that caused by operation of the ventilation, air-conditioning and refrigeration units, was eliminated

to defend herself Though the more severe effects passed off quickly with rest and fresh air, the men were often fatigued and extremely tense for days thereafter

Ventilation and air conditioning were the subjects for critical comment in over four hundred reports, better than half of which offered suggestions for improvement Inadequate and unequal distribution of air between the forward and after compartments of the ship and inadequate cooling capacity of the air-conditioning units were the most common complaints Other frequent criticisms concerned material defects of the air-conditioning apparatus, the hazards of ventilation in heavy weather, and inadequacy of ventilation when submerged The majority of reports concerning auxiliary ventilation and cooling installations were favorable, although it was sometimes noted that the devices failed to compensate for the basic inadequacies described previously

Cold and Habitability—Poor living conditions often prevailed on cold water operations

The torpedo rooms were very wet Metal fittings throughout the ship sweated constantly Heaters had to be used sparingly to conserve the batteries With sea water at temperatures of 27 F (— 28 C), single hull portions of the ship were impossible to heat There was constantly ice in the torpedo room bilges, and pipes containing water, such as shower drains, were frozen solid

Excess Carbon Dioxide and Oxygen Depletion—Limiting values of oxygen and carbon dioxide, after the ship had submerged, were theoretically not attained until the expiration of a period of hours calculated from a formula which, although adjustable, was derived on the basis of peacetime complements and operating conditions Adequate instruments to measure the amount of carbon dioxide and oxygen were not available Need for purification of air was commonly based on subjective evidence, such as headache, dyspnea, and failure of the air to sustain a flame When the need became obvious, varying amounts of carbon dioxide absorbent, which is caustic and irritative, were spread, the atmosphere was further improved by releasing oxygen or compressed air into the ship

On several patrols, excessive levels of carbon dioxide seriously and adversely affected personnel efficiency For various reasons, it is difficult to correlate reports of increased levels of this agent with those of associated symptoms With this in mind and considering the eighty-nine reports containing adequate data, various factors are apparent

The formula used for calculating the time-limiting values of carbon dioxide and oxygen was not always applicable to wartime operations, the time at which symptoms of intolerance became evident did not necessarily follow the calculated time In twenty-two of twenty-six reports, the actual period of acceptability of the air ran from one to six hours less than the calculated figure Half the reports came from

patrols made in northern areas of operations where, because of weather conditions and long hours of daylight, prolonged submerged operations were common. Moreover, the ships were cold and damp, requiring more exertion on the part of each man to keep warm. These factors, in addition to the routine and the increased complement, made it necessary to revitalize the atmosphere frequently.

Purification of air was also a matter of particular concern aboard submarines used as troop transports. On the fifth patrol of the N, when 109 Army Scouts (in addition to the crew of 96) were transported in the Aleutian area, perilous levels of carbon dioxide were experienced, particularly when the Scouts were making ready to disembark. The day preparations were made to land, the level rose to 4 per cent. This defect of habitability, in conjunction with the overcrowding, the cold and the heavy condensation, no doubt explains the statement "Delay from day to day had a severe effect on most of the Army Scouts."

Much fundamental and careful research has been carried out concerning the physical and mental effects of anoxia and of carbon dioxide poisoning. Studies have been made to improve the available methods of air purification and of detection of undesirable changes in the atmosphere. There was need for positive application of the resultant knowledge to improve submarine habitability, today, with the advent of "schnorchelling,"³ the need is even greater. The development of an instrument panel in the control room, which would record at all times the oxygen, carbon dioxide, carbon monoxide, hydrogen and hydrocarbon content of the submarine's atmosphere, together with the temperature and the relative humidity, would be a real step forward. It would obviate the necessity of relying on variable subjective symptomatology, inaccurate formulas and obsolete equipment for such fundamental data.

Toxic Gases—Toxic gases are commonly thought to be a hazard on submarines. It is true that carbon tetrachloride, when used as a cleaning agent, produced distressing and disabling physical effects, for this reason, its use was abolished. Although the formation of chlorine gas, especially after flooding of torpedo battery compartments, was not uncommon, only two serious encounters with it occurred. Formation of arsine and stibine gases in detectable and detrimental quantities was not experienced. Methods for eliminating hydrogen were apparently satisfactory. Thus, the problem of toxic gases aboard submarines is seen to have been more potential than actual in World War II. Of much greater significance were the relatively simple factors of extreme heat and humidity.

3 "Schnorchelling" is the obtaining of air for the Diesel engines from above the surface of the water when the submarine is submerged.

Fires—The relation between fires and habitability was important. The dense, black clouds of smoke quickly spread throughout the compartments. The acrid, phenolic fumes were not only irritating and blinding but also extremely nauseating. With the intense heat, compartments quickly became untenable. The toxic, blinding and demoralizing effect of smoke emphasizes the necessity for thorough and frequent instruction in the operation of protective equipment, without which men may be quickly overcome. Adequate and effective firefighting equipment is a necessity.

Potable Water Supply—In the early days of the war, limitation of fresh water was cause for great concern and was a factor limiting the duration of a few patrols. Fortunately, evaporating units of today are reliable in service and are capable of producing an entirely adequate supply of fresh water.

Condensate from the air-conditioning apparatus was used to augment the supply of fresh water. Dr. George Schiff made a war patrol aboard a submarine to study the problem and concluded that by filtration sufficient condensate could be chemically and bacteriologically purified to make 300 gallons available for daily general use. Condensate was utilized for bathing, in washing machines and for general cleaning. Various methods of collection and storage were in use. In view of the critical nature of weight and space aboard submarines there were no authorized provisions for storage beyond installation of a 20 gallon tank for collection of condensate to be used in washing machines.

Impairment of potability of fresh water sometimes occurred. On a number of patrols, contamination with copper sulfate took place at levels sufficient to impair efficiency of personnel, it was the cause of termination of one patrol. It appears reasonably certain (from investigations carried out at the Naval Medical Research Institute) that copper and nickel were derived from the action of vapor and hot water on the metal tubes in the stills. Future arrangements call for their replacement by tubes coated with tin. When this is done, contamination of water with copper sulfate may be important only historically.

Submarine Ration—The inherent limitations and discomforts of life aboard submarines made imperative special efforts to provide a good ration. Food was excellent and deserved the reputation which it came to have among other less elaborately fed branches of the service. Certain problems existed, however. More active participation by squadron medical officers is needed to assure submarines of a satisfactory ration. The whole problem should be investigated with a view toward constructing an exact, although flexible, master ration plan. More thorough schooling of commissary officers, stewards, cooks, bakers and

supply officers is indicated. The two dietary factors most commonly the cause for complaint were the quality and amount of boned beef. Submarines should be given a high priority, especially at advanced bases, to obtain frozen fruits and vegetables, whose importance was amply demonstrated. Certain luxury foods are important to provide variety and to enliven what otherwise may be a monotonous diet. The significance and importance of ice cream in providing variety in the diet and as a morale builder are apparent ⁴ from patrol reports.

Sanitary Tank Head System—Waste products from the lavatories and galley were collected in sanitary tanks. Military security prevented emptying of the tanks except on surfacing under cover of darkness, the tanks were then blown dry with compressed air. They could be flushed with sea water only with difficulty. On a long patrol, despite frequent emptying and the use of various disinfectants, the tanks became unpleasantly odorous and were the cause for many justified complaints. Correction of this essentially mechanical defect should not be too difficult. One may conjecture, in this respect, to what extent the present problem might become magnified aboard submarines equipped for schnorchelling and submerged for long periods.

Overcrowding—Bunking facilities aboard many submarines were designed for peacetime complements, which were increased as the war progressed. With the addition of electronic apparatus and new types of torpedoes which required frequent routining, the shortage of space became more and more critical. Adequate provision for bunking and personal needs could not be made. Overcrowding on the average patrol probably produced no lasting effect on personnel efficiency. On submarines used in air-sea rescue operations and as troop transports, serious overcrowding was experienced. In preparing for the future, the use of submarines for such purposes merits review in the light of lessons so recently learned.

Protective Clothing—To maintain a reasonably long and alert watch in the most severe weather, bridge personnel must remain comfortably warm and dry. Adequate protection of the face, hands and feet is fundamental. On cold water operations it was apparent that the available items of protective clothing were woefully inadequate. Production of improved garments, with the special needs of the submarine service in mind, should be investigated. Designs of clothing must be practical and tailoring neat, with a minimum of bulk, to facilitate rapid and easy clearance of the bridge and easy stowage. Material must incor-

⁴ Shilling, C. W., and Duff, I. F. Analysis of Submarine Food Problems in World War II, U. S. Nav. M. Bull. 48 683-697 (Sept-Oct) 1948.

porate a minimum of weight and bulk and a maximum of durability, practicability and safety, it should have rapid drying qualities. Great merit exists in the recommendation for a satisfactory one piece exposure suit.

OTHER FACTORS INFLUENCING PERSONNEL ENDURANCE

Length of Operations—In 1941 and 1942, little was known concerning the length of war patrols which men might be expected to tolerate. Accumulated experience tended to modify some of the earlier impressions.

At the time of leaving the area of concentrated activities, an attempt was made by the commanding officer to estimate the remaining days of personnel endurance. The figure was arrived at subjectively. Though it was reported as "0" days on twenty-five patrols, such an evaluation did not necessarily mean that the crew was in a state of collapse, but rather that the men were no longer on their toes and that their fighting efficiency had dropped. Early evidence of fatigue was commonly observed about the fortieth to the fiftieth day on station.

A patrol carried out in good weather with plenty of targets, good fire control and freedom from depth charges could last far longer than one on which any of these features was missing. The monotony of a submerged patrol without contacts was extremely fatiguing unless some diversion or change of pace was introduced. Short, aggressive patrols were said to take as much or more out of the men than did the longer patrols. If lulls in activity occurred, material reduction in efficiency could be forestalled. If not, fatigue began to be apparent. Although aggressiveness and desire to close with the enemy may not have slackened, the fighting edge of the ship was definitely impaired in that the reserve strength of the crew to meet possible emergencies was lacking. Failure to "shift to the second string" under such circumstances was sometimes cause for regret. On such occasions fatigue might become dangerous, the condition of the crew approaching physical and nervous exhaustion. The last week of patrol was generally the hardest. Recuperation during the quiet return voyage was oftentimes noticeable and sometimes acted to create a false impression of the crew's endurance on arrival at port. When fatigue was excessive, recuperation might not take place, especially when considerable action had been experienced in the last week on station.

Extensive surface operations, while inherently decreasing the amount of rest, increased the general well-being of the crew. On prolonged submerged operations, a routine was necessary which kept efficiency at the highest level. Continual rough seas, with "colds," seasickness, need for securing air from the outside and inability to sleep

produced a most depressing effect. Under such circumstances, withdrawing from station for a short rest was authorized.

The question of how long men might efficiently make consecutive patrols was the subject of much interest. There is no all inclusive answer. Some men made an astounding number of war patrols without apparent ill effect. The receipt of "new blood," through the enforced rotation policy, resulted in general improvement in spirit and workmanship, which was conducive to an aggressive spirit and to a closely integrated crew.

Morale—A high state of interest and aggressive determination was essential to the success of operating submarines and was closely related to personnel endurance and morale. The greatest single factor contributing to a high state of morale was successful engagement with the enemy. Once a new ship had successfully completed a patrol, the battle had been half won. All hands then felt their footing to be secure, for they had ceased to be a "detail" and were, instead, a fighting unit. There was nothing so shocking as a "zero run," especially to the crew of a ship with a long record of success. On patrols characterized by disappointment, lost opportunities and lack of worthwhile contacts, poor performance of the deck watch might be observed. As the war progressed and targets became less common, the "lethargy of long diving days, of rough sleepless nights and limited exercise had to be mitigated by a clear portrayal of the part submariners were playing in the over-all strategic and tactical plans." The highest qualities of leadership on the part of the officers and alert patience on the part of all hands were essential.

There were many "creature comforts" which were vital in maintaining morale. These included good food, mail, movies, books, magazines, phonograph and rebroadcast records, adequate quantities of fresh water, mascots, church services, favorable publicity and the possibility of "new construction," with the attendant four to six month period of "States-side" duty. The great importance of adequate and comfortable facilities to permit rest and recuperation at the end of patrols contributed greatly, with the foregoing factors, to the sustained pattern of success which characterized submarine warfare in World War II.

MEDICAL CARE AND FACILITIES AVAILABLE TO SUBMARINES

The advantages of having specially trained medical observers aboard operating submarines for research purposes are obvious, as is the desirability of having a physician attached to one of a group of submarines on air-sea rescue operations. Medical officers especially experienced in submarine medicine are needed at advanced bases, where

they should be attached to submarine squadrons. They should familiarize themselves with the ships and develop a close liaison with commanding officers and pharmacist's mates. Certain medical conditions (unusual fatigue, chronic recurrent appendicitis, chronic seasickness, inability to equalize for increased pressure, active venereal disease, tuberculosis) should be detected and corrected, for they not only may be disqualifying but may interfere with personnel efficiency. Men showing evidence of emotional tension must be carefully evaluated before being permitted to return to submarines. Transfer at sea of injured and ill personnel was frequently necessary, and facilities to accomplish this rapidly and safely under the most adverse conditions must be available.

SUMMARY

The reports of fourteen hundred and seventy-one submarine war patrols made during World War II have been studied to evaluate the human factor in problems of submarine combat.

No health problems entirely peculiar to the submarine service exist. As in all other branches of the military forces, the commonest causes of man-days lost aboard submarines on combat patrol were acute infections of the upper respiratory tract, injuries, and diseases of the gastrointestinal system. That not a single death occurred from appendicitis originating on a war patrol is attributable to intelligent medical care by well trained pharmacist's mates.

In the nearly four years of the war, only 62 deaths from all causes (including battle injuries) occurred aboard submarines on patrol, exclusive of those lost on overdue ships. While the health of submarine personnel was generally excellent, it is significant that serious individual or mass illness terminated or interrupted twenty-nine of fourteen hundred and seventy-one patrols.

Despite the special hazards under which submarine crews lived and fought, which are popularly thought to contribute to psychiatric breakdown, the actual psychiatric casualty rate, as shown in the reports, was amazingly low. This record is essentially a reflection of careful selection of personnel.

The medical problems peculiar to submarines arise from unfavorable changes in habitability, which occur chiefly in combat. The most important of these are excess heat and humidity, the accumulation of carbon dioxide and the depletion of oxygen from the air. That only thirty-one patrols in World War II were interrupted or terminated because of these or other deficiencies of habitability speaks well for the progress which was made in control of these problems. Until these deficiencies have been completely overcome, they will continue to be a limiting factor in submarine operations.

TRAUMATIC CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

Postmortem Study

HYMAN LEVY, M D

NEW YORK

IN THE rapidly expanding literature on nonpenetrating injury to the human heart, there is scant reference to direct damage to the coronary arteries by such blunt injury. A rare case of this type, with detailed clinical and postmortem studies, is reported at some length, as it appears to be an authenticated instance of thrombosis of the coronary artery with consequent myocardial infarction, produced by a contusion of the anterior wall of the chest.

REPORT OF A CASE

C B, a woman, was first admitted to the Mount Sinai Hospital in November 1945, when she was 49 years of age. Renal disease of unspecified type developed at the age of 31, during her second pregnancy. At the age of 37, a laparotomy was performed with the removal of a pelvic tumor, postoperative radiation treatment was given. Early in 1945, hypertension was first brought to her attention. The systolic reading was then 200 mm of mercury. Three days prior to her first admission to the hospital in November 1945 she felt faint, and, on attempting to leave her bed, she collapsed, striking the left side of her face and sustaining multiple bruises. Dizziness and severe headache persisted for the next three days, and she was admitted to the hospital. She was pale and lethargic. The fundi oculorum presented moderately severe vascular changes, with gray nerve heads and diffuse flat edema obscuring the margins of the disks, the arterioles were narrowed. Numerous exudates and hemorrhages were scattered throughout the retinas. The lungs were clear on auscultation. The apical impulse was forceful and was felt in the fifth interspace. The heart sounds were of good quality. A systolic murmur was heard at the apex. The basic second sounds were of equal intensity. The blood pressure was 240 systolic and 115 diastolic. The electrocardiogram (fig 1) showed regular sinus rhythm, a diphasic T wave in lead I and a shallow T wave in lead II. Roentgenographic examination of the chest revealed slight enlargement of the left ventricle. The circulation time, arm vein to tongue, by the calcium gluconate method, was 14 seconds. The circulation time from arm vein to lung by the ether method was 7 seconds. Both readings were within normal limits for these methods. The venous pressure was normal, measuring 75 mm of water. Lumbar puncture was readily performed and showed fresh blood, evidence of recent subarachnoid bleeding. Treatment consisted of sedation, the use of the Kempner rice diet, magnesium sulfate by mouth and hypertonic glucose solution intravenously. On this regimen, the blood pressure slowly dropped

From the Medical Service of Dr George Baehr, Mount Sinai Hospital

and the headache remitted. The patient was discharged from the hospital on the twenty-seventh day, having weakness and asynergy of the left upper extremity as the residua of the cerebrovascular insult she had undergone shortly before her admission.

During the ensuing eight months, she remained in relatively good health, complaining only of some weakness of the affected extremity and slight dyspnea on exertion. On Sept 10, 1946, she was driven by her son into the country. The driver lost control of the automobile, which crashed into a telephone pole. The patient, seated in the rear of the car, was thrown forcibly forward against the back of the front seat, resulting in a contusion of the anterior wall of the chest. There was no loss of consciousness. Her first recollection was of squeezing pain in the left side of the chest and of some difficulty in catching her breath. She later

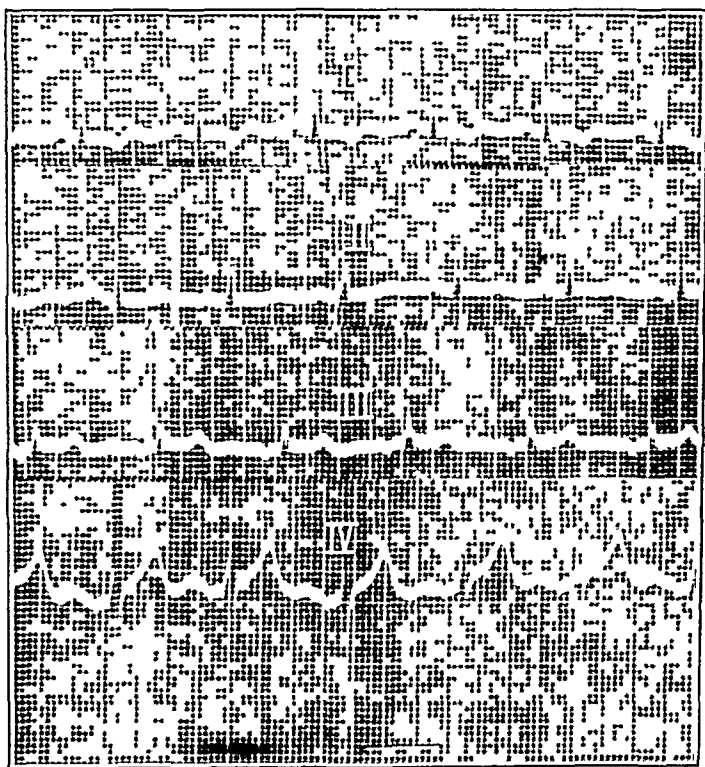


Fig 1—Electrocardiogram taken Nov 8, 1945 during patient's first admission to the hospital. The changes in the T wave are those commonly seen in hypertension.

described the sensation as a feeling that "two bones were being squeezed together." After preliminary roentgenographic examinations at a nearby hospital proved negative for skull fracture, she was brought to the Mount Sinai Hospital, eight hours after the accident. On examination much bruising was in evidence, especially about the left midchest and the left orbital area. The pupils were round and regular and reacted to light and in accommodation. The right fundus was visualized and showed narrowed, tortuous arterioles. The margins of the disk were clear. A few small hemorrhages were seen. A large ecchymosis, of the size of a football, occupied the left anterior wall of the chest, close to the sternum (fig 2). The apical impulse was again felt in the fifth interspace, slightly to the left of the midclavicular line. Gallop rhythm was present. A systolic murmur was

heard at the apex. Minor lacerations, bruises and ecchymoses were distributed over the extremities.

The first electrocardiogram (fig 3) was taken on the day following the patient's admission to the hospital. It showed sinus tachycardia and the rate of 105 beats per minute, with a small Q wave in lead I and a deep Q wave in lead IV. The RS-T segments in leads I and IV were elevated. The RS-T segment in lead III was depressed. The T waves in leads I and IV were depressed. These changes are typical of acute coronary thrombosis with myocardial infarction of the anterior wall of the left ventricle.

On this same day, the white blood cells numbered 10,900, with 83 per cent polymorphonuclear forms. Other laboratory findings included a bleeding time of 3 minutes. The clotting time was $7\frac{1}{2}$ minutes (Lee-White method). The prothrombin index was 100 per cent, the control and prothrombin time both being 16 seconds. The icteric index was 3. The ascorbic acid level of the blood was 7.8 gamma per cubic centimeter of serum. The reaction to the tourniquet test was weakly positive. The thrombocyte count was 210,000 per cubic millimeter.

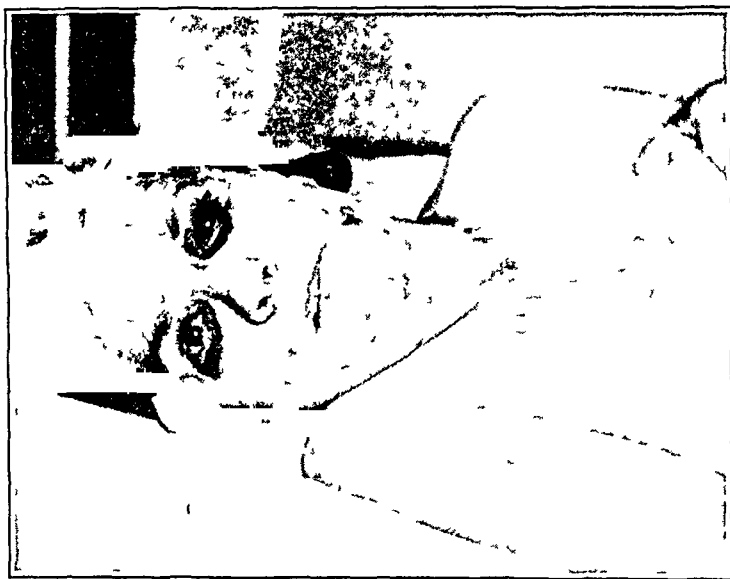


Fig 2—Photograph of patient, in bed, one week after accident, showing large ecchymosis of anterior wall of the chest.

The sedimentation rate of the red blood cells on the third day after admission was 39 mm per hour (Westergren method). The blood urea nitrogen was 14 mg, blood sugar 85 mg, total cholesterol 435 mg and total serum protein 8 mg per hundred cubic centimeters. The specific gravity of the urine ranged from 1.018 to 1.022. The urine gave a 1 plus reaction for albumin, there was no glycosuria. The pain experienced immediately after the accident persisted in variable degree for two days, and on the third day the patient was free from pain in the chest. Gallop rhythm was still present, however. She lay quietly in bed, neither dyspneic nor orthopneic. The temperature remained elevated for the first six days, slowly dropped to normal in the next two days and remained normal for the last four days.

Another electrocardiogram (fig 4), taken on the tenth day after admission, showed the return of the R-T segment to the isoelectric line in lead I, with inversion of the T wave, a deep Q wave and some elevation of the R-T segment remained in lead IV. Routine hospital rounds on the morning of the thirteenth day found the patient comfortable. The lungs were clear on auscultation, the cardiac rhythm was regular. The heart sounds were of good quality and the

gallop was no longer heard. The cardiac rate was 88 beats per minute. Three hours later, at noon, she was observed by the nurse to be in a convulsive seizure. There were generalized tonic convulsions and apnea. Artificial respiration, as well as intracardiac drug therapy, was of no avail in restoring cardiac function. The heart sounds and pulse were unobtainable prior to the failure of respiration.

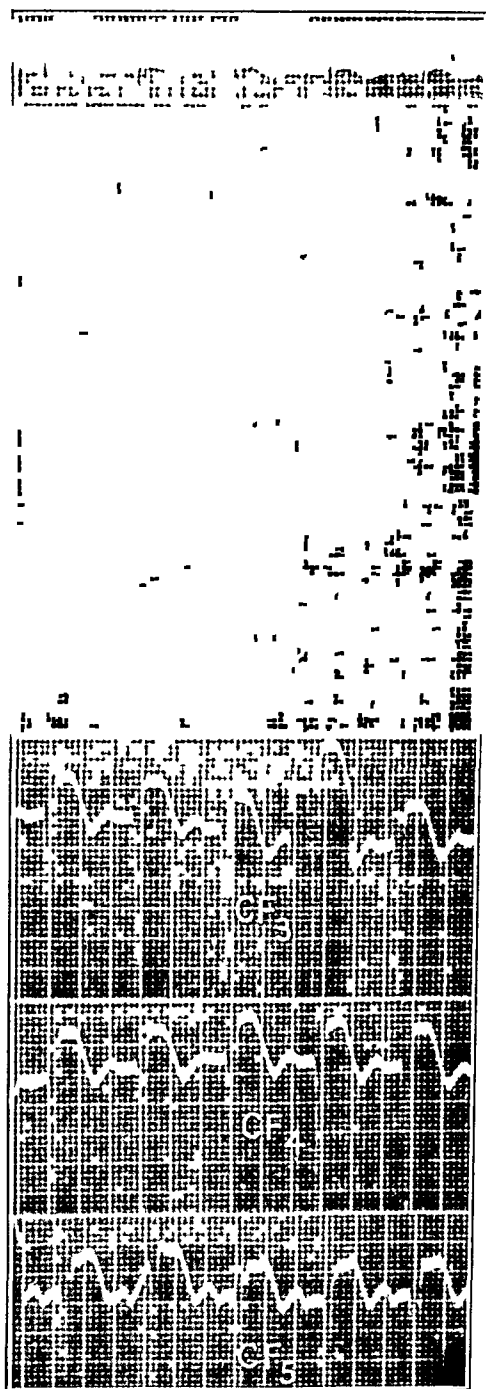


Fig 3—Electrocardiogram taken on the day after accident. Q waves are seen in lead I and the precordial leads, with elevated R-T transitions, on the basis of which diagnosis of coronary thrombosis with infarction was made.

Autopsy was performed five hours after death. Numerous areas of ecchymosis were evident over various parts of the body, especially about the orbits. On the anterior wall of the chest, in the precordial area, a large, irregular ecchymosis, measuring 6 by 8 cm, was visible. No costal fracture could be made out. The right pleural cavity contained 300 cc of clear straw-colored fluid, 200 cc of a similar fluid was obtained from the left pleural cavity. The right lung was adherent to the fourth, fifth and sixth ribs laterally by firm fibrous bands. The remainder of the pleural surface was smooth. The pericardial surfaces were smooth and glistening. A small quantity of pericardial fluid, blood stained and about normal in amount, was present. The heart weighed 410 Gm. Several needle punctures were seen, the evidence of intracardiac therapy. No ecchymoses were apparent on

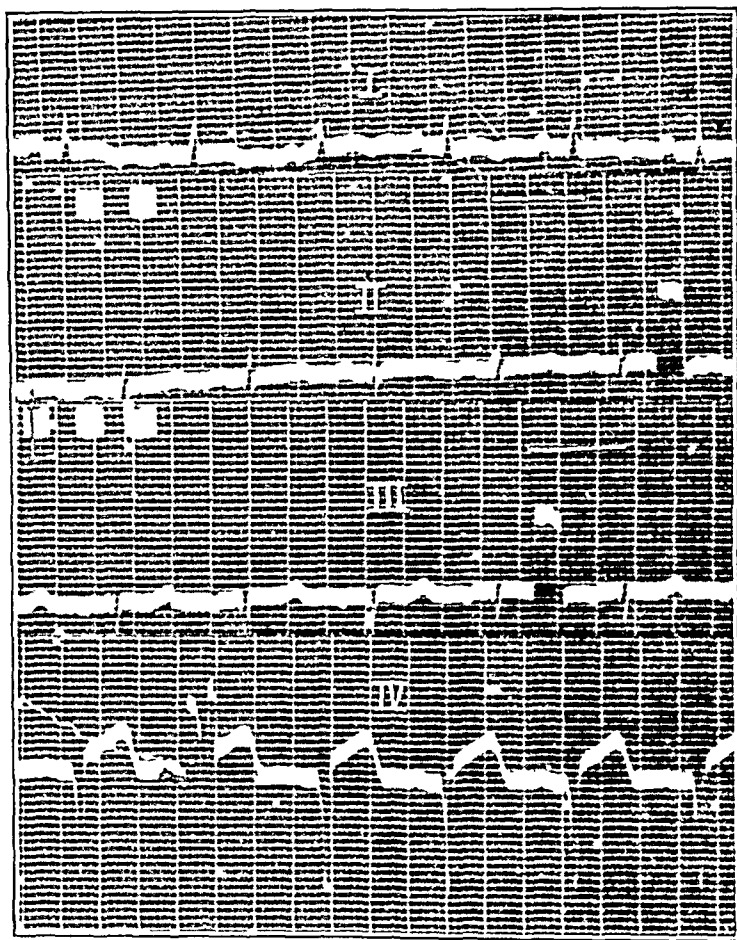


Fig 4—Electrocardiogram taken on the tenth day after the accident, showing progressive changes of myocardial infarction

the surface of the heart. A large myocardial infarct was present and comprised the anterior half of the interventricular septum, the lower half of the anterior wall and the entire apex. These areas showed widespread confluent necrosis surrounded by red zones. Within the infarcted area on the anterior apical surface there was a depressed, irregular, dark red, mottled zone, measuring 5 by 4 cm. Two similar areas, 1.5 cm in size, were present on the posterior surface of the apex, on either side of the septum. The myocardium and the endocardium of the auricles were not noteworthy.

The right ventricular wall measured 3 to 4 mm posteriorly. The lower portion of the septum showed yellow discoloration of the trabeculae. Within the

anterior cusp of the tricuspid valve was a 5 mm hemorrhage. The tricuspid ring measured 9.5 cm. The pulmonary valve was not remarkable, its ring measured 6.5 cm. The mitral valve was essentially normal, its ring measuring 7.5 cm. The left ventricular wall was unusually thick and firm, measuring 2 cm. On horizontal section through the anterior wall and septum, the necrosis was seen extending up to a level of 4 cm from the origin of the left main coronary artery. Higher sections showed that the reddish depressed areas of repair extended up to a level

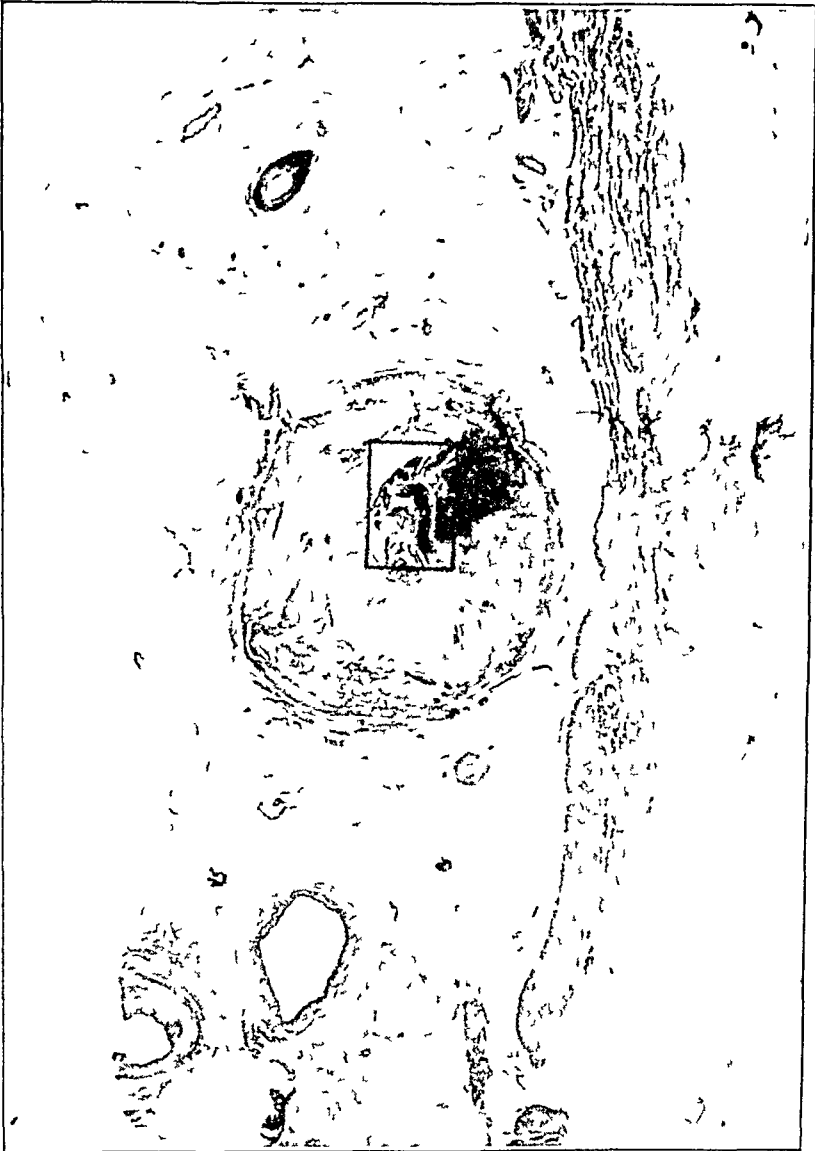


Fig. 5—Photomicrograph of transverse section of the descending branch of the left coronary artery at site of thrombosis, showing the large subintimal hemorrhage, $\times 79$

2 cm from the orifice, where they involved the myocardium without reaching the subpericardial fat tissue.

The left anterior descending artery was occluded completely by red and gray adherent material, beginning 3 cm from the orifice and extending for a distance of 1 cm. On cross section, the lumen was occluded mainly by a dark red material

On one side this material was completely separated from the wall of the vessel by a thin, circular, gray layer. Between this zone and the vessel wall a yellowish white substance was present. Proximal and distal to the site of occlusion the artery showed advanced sclerosis and calcification with narrowing. The left circumflex and the right coronary arteries were about one-half the size of the left coronary artery. The aorta presented pronounced intimal sclerosis and thickening with elevated yellowish white patches.



Fig 6—High power magnification of blocked-off area in figure 5, showing thrombus (A), rupture of intimal lining (B), and subintimal hemorrhage (C), $\times 74$

The lungs showed no evidences of laceration. There were firm fibrous adhesions of both lungs, obliterating the interlobar fissures. The basal portion of the lower lobe of the left lung and the entire lower lobe and the middle lobe of the right lung were purple, fleshy and airless. There was considerable oozing of frothy blood

from the freshly cut sections of the lung. The pulmonary vessels appeared normal. Other observations included hydronephrotic contraction of the left kidney, secondary to intrinsic constriction of the left ureter by old scar tissue, stenosis of the recto-sigmoid portion of the intestine due to the same cause, amyloidosis of the glomeruli and of the arterioles of the heart, liver, spleen, pancreas, kidney and adrenal glands.

Finally, the brain showed severe arteriosclerosis of the vessels of the cerebrum, cerebellum and spinal cord, with encephalomalacia and scarring in the cerebellum. In the left cerebellar hemisphere at the point where the middle cerebellar peduncle meets the white matter of that hemisphere, a triangular defect was observed, measuring about 6 cm. Its lining was yellowish, and it was surrounded by a narrow zone of yellowish tissue. This yellow zone could be traced into the lateral wall and roof of the fourth ventricle. This was an old area of softening with hemorrhage and extravasation of blood into the ventricular system. The blood vessels in this affected area showed prominent changes—hyalinization of the vessel walls and occlusion of many small vessels and capillaries. The walls of the larger vessels were thickened, and thrombus formation was evident. The changes in the blood vessels of the cerebral cortex and of the spinal cord were similar, although less extensive.

Microscopic examination of a section of the left ventricle revealed early acute myomalacia, with large islands of muscle showing loss of striation and of nuclei and surrounded by fibroblastic and capillary proliferation. Section of the interventricular septum showed acute myomalacia, with replacement of necrotic muscle fibers by loose fibrous tissue, capillaries and infiltration of round cells. The left anterior descending branch of the left main coronary artery was decidedly atherosclerotic, and there was a hemorrhage into an atherosclerotic plaque (fig 5). The extremely narrowed lumen was occluded by a recent thrombus (fig 6). Both the myocardial infarct and the occluding thrombus were of a histologic age consistent with the time elapsed from the day of the accident to the day of death, namely, thirteen days.

COMMENT

It is now generally accepted that nonpenetrating blows to the chest can cause myocardial damage. There is ample evidence, both experimental and clinical, to support this view. The experimental investigations of Schlomka¹ demonstrated that lesions of the cardiac muscle can be produced by blows delivered to the chest of animals. Using cats and rabbits for the most part, Schlomka struck blows of moderate severity to the unexposed wall of the chest. In some animals, he observed localized myocardial hemorrhage and, more rarely, tears into the wall of the heart muscle. He was of the opinion that localized blows transmitted to the precordium induced spasm of the coronary arteries in much the same manner that gunshot wounds of the extremities cause traumatic segmental arterial spasm when penetration of the tissue is close to the artery. To this spasm of the coronary arteries and the resulting myocardial ischemia, Schlomka ascribed the functional and anatomic alterations noted. Functional changes included various types of arrhythmia, heart block and electrocardiographic abnormalities, many of which were transient.

¹ Schlomka, I. *Commotio cordis und ihre Folgen*, *Ergebn d inn Med u Kinderh* 47 1, 1934.

In the experimental study of Kissane, Fidler and Koons,² blows were delivered to the unexposed chests of anesthetized dogs. The cardiac lesions produced were chiefly subendocardial and pericardial hemorrhages. These hemorrhages varied from small petechia-like spots to large areas of bruising and discoloration. The myocardial hemorrhages and contusions were also seen to extend into the muscle wall from the local areas of bruising on the pericardium and the subendocardium. In some of the dogs, pericardial tears were observed. The authors postulated edema of the heart muscle to account for the sudden and transient electrocardiographic changes seen in several of the animals in which no cardiac lesions were observed at autopsy.

From clinical studies of nonpenetrating trauma to the chest one can draw on cases which illustrate the wide range of cardiac injuries, from the mildest contusion, with minimal signs and symptoms which are often overlooked, to rapidly fatal rupture with cardiac tamponade. In 1935, Bright and Beck³ collected from the literature all the cases of nonpenetrating cardiac injuries and grouped them under three headings. In the first group, numbering 12 cases, the accident was survived but cardiac failure and irregularities in rhythm were exhibited. The second group comprised 11 cases in which death was due to cardiac failure. The third group included 152 cases of cardiac rupture, all established by necropsy.

Cardiac rupture may occur during the second week after injury, at the time of greatest softening of the contused muscle. Such was the sequence of events in the case reported by Tuohy and Berdez.⁴ A 63 year old man was injured in a steering wheel accident. He continued to be ambulatory, although he complained of faintness and vomited daily. Two weeks after the accident, while he was in a motion picture theater, he collapsed immediately after a hearty laugh and was taken from the theater dead. Autopsy revealed rupture of the left ventricle near the apex.

Equally dramatic is the story of the 9 year old boy whose chest was pressed against a wall by a cart.⁵ Examination soon after the accident failed to show evidences of external injuries. There were no fractured ribs. As the boy felt quite well on the following day, he was permitted to return to school, where he engaged in the usual games without discomfort. During the next ten days he made no complaints, but on

2 Kissane, R. W., Fidler, R. S., and Koons, R. A. Electrocardiographic Changes Following External Chest Injuries to Dogs, *Ann Int Med* **11** 907, 1937.

3 Bright, E. F., and Beck, C. S. Nonpenetrating Wounds of the Heart, *Am Heart J* **10** 293, 1935.

4 Tuohy, E. L., and Berdez, G. Two Instances of Perforation of the Heart Following Non-Penetrating Chest Injury, *Minnesota Med* **9** 144, 1926.

5 Gunewardene, H. O. Traumatic Rupture of Heart Without External Injuries, *Brit M J* **2** 942, 1934.

the eleventh day after the injury while playing at school, he experienced precordial pain, collapsed and died. At postmortem examination, hemothorax and rupture of the anterior surface of the left ventricle were observed.

The mechanism of cardiac damage in such cases is clear. The force of the external violence is transmitted to the heart muscle, which undergoes varying degrees of reaction depending on the intensity of the impact. In milder injuries, small contused areas with focal hemorrhage may be the only pathologic change, giving rise to few, if any, symptoms. At times, transient arrhythmias and evanescent electrocardiographic changes occur. The most violent blows cause such disruption of muscle fibers as to lead to either immediate or delayed rupture. Between these extremes are many recorded cases of myocardial damage with areas of thinning and aneurysmal dilatation of the ventricular wall, death occurring at some time remote from the accident. While the sequence of events in these remote cases might be open to question in some instances, there are on record illustrations such as the following ones, in which the pathologic changes unquestionably are related to the injury.

A boy 12 years of age was run over by a wagon and had multiple fractures of the ribs on the left side.⁶ Except for occasional attacks of palpitation and vomiting, he remained in good health to the age of 24, when paroxysmal auricular flutter set in, during these attacks, heart failure developed. He died suddenly at the age of 25. Autopsy disclosed a large aneurysm at the apex of the left ventricle. The anterior descending branch of the left coronary artery was interrupted at the upper limit of the aneurysm. One can only surmise whether the artery was damaged directly by the blow, leading to thrombosis of the artery with cardiac infarction and aneurysm, or whether both the artery and the adjacent muscle wall were destroyed by the trauma. There seems little doubt of the relation of the trauma to the observations at autopsy in this young man.

Direct trauma to the coronary arteries with the formation of coronary thrombosis and secondary myocardial infarction has been repeatedly considered a probable mechanism in cardiac trauma. A priori, there is no reason that these vessels, lying superficially on the muscle wall, should not be subject to direct damage, particularly when diseased and brittle. But to date, records of such an accident in which the observations are beyond question are few. However, several reports of lesions seen at autopsy strongly suggest this mechanism of muscle damage.

6 Joachim, H., and Mays, A. T. A Case of Cardiac Aneurysm Probably of Traumatic Origin, *Am Heart J* 2: 682, 1927.

Schminke⁷ reported the history of a 45 year old man who was struck by a wagon shaft. After a short period of unconsciousness, he complained of severe pain in the chest and left arm. For the next six months he continued to experience pain in the chest provoked by climbing stairs and other forms of activity. He died suddenly six months after the accident. Autopsy revealed organized thrombi in the anterior descending branch of the left coronary artery and in the circumflex branch of the right coronary artery. Extensive myocardial scarring with an aneurysm at the apex of the left ventricle was evident.

Damage to the coronary arteries is referred to in Warburg's monograph⁸. One reference is the case just cited. In a subsequent report dealing with the same subject,⁹ Warburg mentioned other cases which came to his attention. One was reported by Fraenkel in 1917¹⁰. A 20 year old soldier died in cardiac failure six months after being injured in a shell explosion. At autopsy, an aneurysm of the left ventricle was observed. The descending branch of the left coronary artery showed aneurysmal dilatation and was blocked by a thrombus.

Warburg⁹ further detailed a personal communication from Muller concerning a man aged 59, who was struck by a bicycle and fell on his chest and abdomen. He subsequently complained of substernal oppression which appeared when he walked up stairs or climbed stairs. On the ninth day after the accident, he had a severe nocturnal attack of angina pectoris, this was followed by fever, leukocytosis and typical changes in the R-T segment in the electrocardiogram which justified the diagnosis of coronary thrombosis. Two weeks after the accident, the patient died in cardiac failure. Necropsy revealed thrombotic occlusion of the descending branch of the left coronary artery with a large infarct and recent pericarditis. There was arteriosclerosis of the occluded branch, and to a lesser degree of the other branches. Further details were not given. It must be assumed that the examiner considered the age of the thrombus and the infarct to correspond with the date of injury. If so, the case history is similar to the one being reported.

Randerath¹¹ cited the history of a 34 year old soccer player who was struck in the chest by a ball kicked from a distance of 5 meters. He

7 Schminke, A. Beitrag zur traumatischen Aetiologie der Arteriosklerose, *Deutsches Arch f klin Med* **149** 145, 1925

8 Warburg, E. Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-Penetrating Traumatic Injuries. A Clinical Study, New York, Oxford University Press, 1938

9 Warburg, E. Myocardial and Pericardial Lesions Due to Non-Penetrating Injury, *Brit Heart J* **2**:271, 1940

10 Fraenkel. Herz mit thrombosiertem Aneurysma der linken Kranzarterie, *Deutsche med Wchnschr* **43** 159, 1917

11 Randerath, E. Frühveränderungen des Herzens nach Commotio Cordis, *Verhandl d deutsch path Gesellsch* **30** 163, 1937

immediately collapsed, with pallor and cold sweat. The pulse was small and quick. There was tenderness to the left of the sternum on palpation. On the following day, after a temporary improvement in the circulation, there was recurrent collapse and, at the same time, sudden coldness and pallor of the right lower extremity. The patient died on the second day after the blow to the chest. No electrocardiograms were taken.

Pertinent necropsy observations included slight ecchymosis to the left of the sternum in the region of the fifth and sixth ribs. There was no pericardial effusion, the pericardium was normal. The heart weighed 370 Gm and was soft, particularly at the left ventricular wall. At the apex a small flat recent aneurysm of the left ventricle with fresh mural thrombus was seen. An embolus was described as being lodged in the proximal portion of the descending branch of the left coronary artery. Another embolus was observed at the proximal end of the right coronary artery. Early arteriosclerosis of the coronary arteries was evident. The severest necrosis was located in the wall of the left ventricle. The anterior papillary muscle was ruptured.

Thrombus material was lodged in the right femoral artery. The occlusive lesions of both the coronary arteries and the femoral artery were considered embolic in origin, arising from the mural thrombus within the cavity of the left ventricle. This case is unusual in many respects, particularly in the formation of an early aneurysm of the ventricular wall and the development of emboli, all within two days. Macroscopically, the aneurysm at the apex and the gray color of the endocardium suggested a less acute process than indicated by the history. Microscopically, however, the process appeared to be acute, displaying normal interstitial tissue in areas of extensive necrosis of muscle fibers.

Of 3 cases of traumatic coronary infarction found in a study of 9,629 consecutive postmortem protocols,¹² Bean described briefly the history of a man who fell 8 feet (2.4 meters) from a ladder and struck his chest, fracturing several ribs on the left side. Severe pain was experienced for a day. Death occurred ten weeks after the fall, and at autopsy a fairly recent infarct with early aneurysmal dilatation was observed. The other 2 cases are presumptive examples of traumatic infarction.

A study of such autopsied material gives some insight into the probable frequency of myocardial damage of varying degree due to external violence. There are also many recorded instances in which recovery took place, but in which the injury was followed by classic signs, symptoms and laboratory evidence of acute myocardial infarction.

12 Bean, W. B. Infarction of the Heart. A Morphological and Clinical Appraisal of Three Hundred Cases, I. Predisposing and Precipitating Conditions, *Am Heart J* 14:684, 1937.

The case of the accident with a golf ball has been cited and recited and is now legend¹³ A 57 year old man was struck in the chest by a golf ball He was temporarily shocked but returned to work for the next two days Attacks of angina pectoris occurred on the third day, and an electrocardiogram showed evidence of fresh myocardial infarction

Equally convincing are the cases reported by Kienle,¹⁴ Boas,¹⁵ Sigler¹⁶ and Hecht¹⁷ One cannot deny that each of these reports gives reasonable proof of the presence of myocardial infarction following trauma The immediate development of pain, coupled with disability, fever and electrocardiographic changes, provides fairly indisputable evidence of myocardial infarction with necrosis of muscle But from the clinical history alone one cannot determine the underlying mechanism of the infarction It may be due to coronary thrombosis or to prolonged coronary spasm without obstruction of the lumen, such as is implied in experimental work,¹ or, finally, to severe contusion of the muscle itself without involvement of the coronary arteries either by spasm or by occlusion

Friedberg and Horn¹⁸ observed myocardial infarction without recent coronary thrombosis in 31 per cent of a group of 34 nontraumatic cases, taken from a total of 2,000 autopsies They ascribed the myocardial damage to intense coronary insufficiency, precipitated by abnormally increased demands on the coronary circulation, already compromised by narrowing Moritz and Atkins¹⁹ likewise observed that in 20 human cases with large cicatrized infarcts, the site of remote coronary occlusion could be identified in only 9 instances This is not remarkable in the light of the observations of Friedberg and Horn, and in view of the now generally accepted role of coronary insufficiency due to shock, loss of blood and unusual physical demands on the coronary circulation, in the production of acute muscle necrosis Indeed, in cases of trauma among persons of the older age groups in which shock is a prominent

13 Relation of Myocarditis and Coronary Thrombosis to Trauma, Queries and Minor Notes, *J A M A* **101** 1503 (Nov 4) 1933

14 Kienle, F Klinische und elektrokardiographische Beobachtungen bei traumatischem Hinterwandinfarkt, *Ztschr f Kreislaufforsch* **30** 674, 1938

15 Boas, E P Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort, *J A M A* **112** 1887 (May 13) 1939, Some Immediate Causes of Cardiac Infarction, *Am Heart J* **23** 1, 1942

16 Sigler, L H Trauma of the Heart Due to Nonpenetrating Chest Injuries, *J A M A* **119** 855 (July 11) 1942

17 Hecht, H H Heart Trauma Myocardial Involvement (Contusion) Following a Non-Penetrating Injury to the Chest (Airplane Accident), *Ann Int Med* **27** 126, 1947

18 Friedberg, C K, and Horn, H Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J A M A* **112** 1675 (April 29) 1939

19 Moritz, A R, and Atkins, J P Cardiac Contusion An Experimental and Pathological Study, *Arch Path* **25** 445 (April) 1938

feature, the resulting myomalacia might well be due to coronary insufficiency secondary to shock, and not to either direct injury of the muscle or occlusion of a coronary artery. The problem of differentiating infarction due to direct injury from that secondary to arterial disease becomes the more difficult as the time interval between injury and postmortem examination is lengthened. For its concise presentation, the summary of Moritz and Atkins¹⁹ is quoted in full.

The objective pathologic criteria for distinguishing between a cardiac contusion and a cardiac infarct vary in usefulness according to the age of the lesion. In the case of a recent myocardial lesion, the only evidence that should almost invariably serve to identify an otherwise indeterminate injury as an infarct is the finding of recent coronary occlusion. Pathologic changes more likely to be found in early contusion than in early infarction include massive interstitial hemorrhage, laceration and tissue disorganization. Since all of these changes may be seen following spontaneous rupture of an early infarct, they are not conclusive. In the case of an older myocardial lesion there is no means of distinguishing objectively between contusion and infarction. Deposits of hemosiderin in myocardial scars are more likely to be seen in healed contusions than in healed infarcts, but since hemosiderin is seen occasionally in healed infarcts its presence is not conclusive. Three months after injury hemosiderin is found infrequently in traumatic scars, so that its absence in no way excludes the possibility of a lesion having been of traumatic origin. The presence or absence of remote coronary occlusion does not serve to identify a myocardial scar as having resulted from infarction or contusion inasmuch as a heart the seat of occlusive coronary disease may have a superimposed traumatic lesion and a heart with a large healed infarct may have no demonstrable coronary occlusion. The pathologic characteristics of the scars of myocardial contusion and infarction are frequently identical, and the presumptive nature of their origin must be determined by historical data rather than by postmortem examination.

In the case here reported, clinical data obtained before the accident, as well as results of detailed clinical and postmortem studies made after the injury, were available. The trauma appeared to cause direct injury to a large plaque in the descending branch of the left coronary artery, followed by hemorrhage within the plaque and then seepage of blood through the intimal lining (fig 6) with the development of a thrombus at this site. The early onset of pain in the chest, as well as the results of electrocardiographic examination, indicated that this process must have developed rapidly, with the end stage of occlusion and consequent infarction occurring within a short time after the injury.

The rarity of undoubted traumatic coronary thrombosis is readily confirmed by reference to reports on traumatic and accidental deaths. Hawkes²⁰ in 1935 reviewed the protocols for a ten year period, 1925 to 1934, of all deaths recorded in the Office of Chief Medical Examiner, in Essex County, N. J. Autopsy was performed in 7,000 cases for medicolegal reasons, of these 2,708 were of traumatic deaths, of which

20 Hawkes, S. Z. Traumatic Rupture of the Heart and Intrapericardial Structures, *Am J Surg* 27: 503, 1935.

70 were instances of injury to the heart and great vessels. In only 4 cases was the cardiac injury alone responsible for death. In none was traumatic coronary thrombosis observed. In 262 cases reported by Osborn,²¹ who studied the observations made on persons in fatal accidents, no reference to direct damage to the coronary arteries was included.

Contusion to the heart must be entertained not only in those instances of external evidences of injury but whenever the possibility exists that the heart was traumatized by a blow to the chest, even in the absence of signs of external violence. Discoloration due to bruising of the skin and subcutaneous tissues may not be demonstrable immediately after the accident. The mechanism of contusion by sudden jarring of the heart against the interior of the bony thorax when parts of the body distant from the chest are struck must also be kept in mind.

Clinical symptoms vary considerably in injury to the chest and heart. While the dramatic evidences of shock, with collapse, air hunger, restlessness and pallor, may be present, oftener symptoms are less obvious and so unobtrusive that patients are allowed their usual activity, only to die suddenly from rupture of the heart during the period of softening of the contused muscle. Patients usually do not faint. In Warburg's latest group of 59 cases,⁹ fainting was specified in only 4 instances, while in 24 the absence of fainting was explicitly mentioned. In 10 of this group a latent period of a few days to several months intervened between the time of accident and the appearance of clinical symptoms. Barber²² stated that in his experience a latent period is the rule rather than the exception, as he observed symptomless intervals of twelve hours to three days.

Pain may be a complaint immediately after or at some time subsequent to the accident. It is frequently difficult to differentiate the pain arising in a contused chest wall from that having its origin in bruised cardiac muscle. Shortly after injury, pain may be prolonged and severe in both. Later, the pain of a contused chest tends to be more constant and may last for several days, abating slowly. It is significant that in Warburg's series of 51 cases which were considered to be definitely of traumatic origin on postmortem examination 15 showed no symptoms immediately after the accident to suggest the possibility of injury to the heart.⁸ A slight rise in temperature or an increased rate of sedimentation of the red blood cells may serve to indicate the presence of bruised muscle tissue.

21 Osborn, G. R. Findings in Two Hundred Sixty-Two Fatal Accidents, *Lancet* **2** 277, 1943.

22 Barber, H. The Effects of Trauma Direct and Indirect, on the Heart, *Quart J Med* **13** 137, 1944.

Serial electrocardiograms taken immediately after trauma are indispensable to the diagnosis of cardiac contusion. Electrocardiographic abnormalities may be transient, lasting but a few days. Baiber²² did routine electrocardiograms on all patients admitted with a history of accident, if they were seen within forty-eight hours. Among 75 unselected patients, 20 showed abnormal electrocardiographic tracings. In 1 patient there was no postmortem evidence of myocardial bruising twelve days after the T waves in leads I and II had been flat or slightly inverted. In another patient permanent partial heart block was present. In 17 instances the electrocardiograms returned to normal in a short time, indicating that these abnormalities were the result of the trauma. Such temporary abnormalities were recorded most frequently one or two days after injury. On several occasions, the electrocardiogram, normal a few hours after the accident, showed abnormalities twenty-four or forty-eight hours later. In the severer contusions, electrocardiographic abnormalities similar to those seen in coronary disease with occlusion may occur. Thus, Kissane²³ observed that the changes in the RS-T complex and in the T waves frequently do not occur for twenty-four to forty-eight hours, but that they are similar in every respect to those changes characteristic of coronary occlusion. He also emphasized the importance of repeated electrocardiograms in cases of trauma.

Anderson,²⁴ in reviewing nonpenetrating injuries of the human heart, stated that the electrocardiographic tracings in 30 cases in which abnormalities had been described were in accord with experimental data. The T waves may be unusually large or inverted. The RS-T complex may be either elevated or depressed. Typical coronary T waves may occur and are similar to those observed in coronary thrombosis and in pericarditis with or without effusion. Q waves may be abnormally deep, and the QRS complex may show slurring and notching. The frequency of involvement of the muscle just under the pericardium may account for the same kind of changes in the RS-T complex as are seen in coronary occlusion with infarction.

SUMMARY

A rare instance of thrombosis of a major coronary artery, with consequent myocardial infarction due to contusion of the wall of the chest, is described. The historical, clinical and pathologic data presented leave little doubt as to the role of blunt injury to the chest in producing the lesion described in this case.

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23 Kissane, R W. Cardiac Contusion, in Blumer, A. The Practitioners Library of Medicine and Surgery, 1940 supplement, New York, D Appleton-Century Company, Inc., p 318

24 Anderson, R G. Non-Penetrating Injuries of the Heart, Brit M J 2 307, 1940

CHRONIC NONLEUKEMIC MYELOSIS

Report of Six Cases

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THE NAME "chronic nonleukemic myelosis" seems the most appropriate for certain conditions which have been described in hematologic literature under a wide variety of other names. The term (Mavros, Hickling, Carpenter and Flory¹) is, in the main, merely descriptive, and not even particularly accurate. Other suggested names for the syndrome include "chronic splenomegaly with anaemia and myeloid reaction of the blood" (Emile-Weil and Clerc²), "splenomegaly of the myeloid type without myelocytthemia" (Rathery³), "myeloid megakaryocytic splenomegaly" (Downey and Nordland⁴), "splenomegaly with myeloid transformation" (Tudhope⁵), "hepatolienal hematopoietic endotheliosis" (Lindeboom⁶), and "agnogenic myeloid metaplasia" (Jackson, Parker and Lemon, Reich and Rumsey⁷). All

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1 (a) Mavros, A. *Folia haemat* **43** 323, 1931 (b) Hickling, R. A. *Quart J Med* **6** 253, 1937 (c) Carpenter, G., and Flory, C. M. *Chronic Nonleukemic Myelosis. Report of Case with Megakaryocytic Myeloid Splenomegaly, Leukoerythroblastic Anemia, Generalized Osteosclerosis and Myelofibrosis*, *Arch Int Med* **67** 489 (March) 1941

2 Emile-Weil, P., and Clerc, A. *Semaine med* **22** 373, 1902

3 Rathery, F. *Compt rend Soc de biol* **54** 138, 1902

4 Downey, H., and Nordland M. *Folia haemat* **62** 1 1939

5 Tudhope, G. R. *J Path & Bact* **44** 99, 1937

6 Lindeboom, G. A. *So-Called Aleukemic Megakaryocytic Myelosis*, *Nederl tijdschr v geneesk* **82** 3072, 1938, abstracted, *J A M A* **111** 664 (Aug 13) 1938

7 Jackson, H., Jr., Parker, F., Jr., and Lemon, H. M. *New England J Med* **222** 985, 1940. Reich, C., and Rumsey, W., Jr. *Agnogenic Myeloid Metaplasia of Spleen. Report of Five Cases Illustrating Diagnostic Difficulties and Danger of Splenectomy and Radiation Therapy*, *J A M A* **118** 1200 (April 4) 1942

the names referred to a condition in which there may or may not be anemia, but in which there are usually primitive red and white cells in the peripheral blood, though the great increase in leukocytes characteristic of leukemia is usually absent. The spleen is enlarged, and, at autopsy, foci of extramedullary hemopoiesis may be found in the spleen and liver and to a lesser extent in other organs, such as the kidneys and the lymph nodes. There also are recorded a number of cases of essentially similar conditions, associated with myelosclerosis and myelofibrosis and described as "fibrosis of the bone marrow associated with a leukemoid blood picture" (Mettier and Rusk, Rosenthal and Erf⁸), "myelophthisic splenomegaly" (Ballin and Morse⁹), "megakaryocytic myelosis with osteosclerosis" (Hewer¹⁰), and "aleukemic myelosis with osteosclerosis" (Stephens and Bredeck¹¹). In some cases primitive red and white cells were not reported in the peripheral blood, but it is possible that the blood had not been examined on the number of occasions which McMichael and McNee,¹² in 1936, showed to be essential for the diagnosis. A similar clinical picture was also described by Vaughan,¹³ in 1936, as a "leuco-erythroblastic blood picture," associated with osteosclerosis, myelofibrosis, and with metastasis to bone from malignant tumors, Hodgkin's disease and multiple myelomatosis. In some cases in which autopsy was performed, there was massive myeloid metaplasia of the spleen. In others, the masses were collected into tumor-like nodules and, because of the predominance of megakaryocytes, the condition was called megakaryocytoma of the spleen (Downey and Nordland⁴). Sometimes the giant cells have been present in such numbers as to form a most striking feature. They have been found in the spleen, liver, bone marrow and lymph nodes¹⁴. Extramedullary hemopoiesis has also been observed in other conditions, including pernicious anemia, anemia of severe sepsis, repeated bleeding and many varieties of hemolytic anemia (Wintrobe¹⁵). An interesting report on a case of hemolytic anemia was recently published by Brewster

8 Mettier, S. R., and Rusk, G. Y. *Am J Path* **13** 377, 1937. Rosenthal, N., and Erf, L. A. *Clinical Observations on Osteopetrosis and Myelofibrosis*, *Arch Int Med* **71** 793 (June) 1943.

9 Ballin, M., and Morse, P. F. *Myelophthisic Splenomegaly*, *J A M A* **89** 1671 (Nov. 12) 1927.

10 Hewer, T. F. *J Path & Bact* **45** 383, 1937.

11 Stephens, D. J., and Bredeck, J. F. *Ann Int Med* **6** 1087, 1933.

12 McMichael, J., and McNee, J. W. *Edinburgh M J* **43** 303, 1936.

13 Vaughan, J. M. *J Path & Bact* **42** 541, 1936.

14 Hickling^{1b}, Rathery³, Tudhope⁵, Ballin and Morse⁹, Downey, D., Palmer, M., and Powell, L. *Folia haemat* **41** 55, 1930. Hirsch, E. F. *Generalized Osteosclerosis with Chronic Polycythemia Vera*, *Arch Path* **19** 91 (Jan.) 1935.

15 Wintrobe, M. M. *Clinical Hematology*, ed 2, London, Henry Kimpton, 1946.

and Wollenman¹⁶ The uniform absence of real leukemic infiltrations and the multiplicity of cell types involved in the metaplasia were said to distinguish the condition from true leukemia The association of pronounced erythropoiesis and leukopoiesis with proliferation of giant cells distinguished the condition from that described by others (Stengel, Wilson, Kettle, Ross¹⁷), in which there was proliferation of giant cells only (Vaughan and Harrison¹⁸) In these two types, it was not always possible to determine whether or not myelosclerosis or myelofibrosis was associated, but it is striking that patients with massive myeloid splenomegaly and osteosclerosis showed the same variations in the duration of the disease and in the type of blood picture as did those with myeloid splenomegaly without osteosclerosis In both groups, there were acute and chronic cases, in both groups, immature cells were usually present in the circulating blood, though rarely they were not, and in both groups, the blood could be said to have been "leukemic," that is, there was often a great increase in the number of circulating leukocytes, a high proportion of which were frequently immature (Hickling^{1b})

I have been able to study 6 cases of this syndrome, in 2 of which autopsy reports were at my disposal Available hematologic data in these cases, with reports of examinations of the bone marrow, are given after the case histories

REPORT OF CASES

CASE 1—History—A white woman of 65 was first seen in 1943, when she complained of a lump in the left side of the abdomen She stated that she had been aware of the lump for at least five years It had never actually been painful, but it appeared to be increasing gradually in size and had recently become uncomfortably large The patient had no cough, but she had lost about 20 pounds (9.1 Kg) in the previous few months She had also felt a little weaker and had experienced some dyspnea on exertion There was a history of an itchy cutaneous eruption, not unlike urticaria It had lasted a few days and had then disappeared The previous history was noncontributory The patient had never had malaria

Examination—The general condition of the patient was good The mucous membranes were reasonably well colored, and there was no obvious loss of weight The cardiovascular system was apparently normal The blood pressure was 160 systolic and 90 diastolic There were no murmurs

The spleen was enlarged, extending almost into the left iliac fossa, and was firm and not tender The liver was also firm and extended 3 fingerbreadths below the costal margin, it was not tender There were no enlarged lymph nodes The

16 Brewster, H H, and Wollenman, O J New England J Med **227** 822, 1942

17 Stengel, A Tr A Am Physicians **19** 174, 1904 Wilson, L B Surg, Gynec & Obst **16** 240, 1913 Kettle, E H J Path. & Bact **23** 413, 1920 Ross, J M J Path & Bact **37** 311, 1933

18 Vaughan, J M, and Harrison, C V J Path & Bact **48** 339, 1939

urine was normal, and there were no significant findings in any of the other systems. The result of the examination of the bone marrow was reported as normal.

Course—The patient was subsequently readmitted to the hospital on a number of occasions, the only notable additional symptoms were episodes of pain in the right loin and associated hematuria. In addition, the spleen had increased still further in size, almost to the point of entering the pelvis. Irradiation of the spleen was begun in 1945, when 3,975 r were given in three months. In 1946, 4,225 r were given, centering over the lumbar spine, and in 1947, 925 r were directed to the spleen. The therapeutic maneuvers resulted in a decrease in the size of the spleen (it then extended about 3 fingerbreadths below the umbilicus) and depressed the level of the white cell count. The dragging weight of the spleen became less severe.

The patient grew gradually weaker during 1947 and complained of severe pain in the right loin and of dysuria. Albumin and blood were present in the urine. The patient died during July 1947. The blood (tables 1 and 2) at no time showed any anemia, but there was a gross increase in polymorphonuclear leukocytes in the peripheral blood, thrombocytosis and occasional normoblasts were noted. A second examination of the bone marrow also indicated that it was normal and not leukemic.

Autopsy (performed by Dr G. Selzer nine hours after death)—The lymph nodes were not enlarged. The spleen weighed 1,342 Gm. It showed extensive "sugar icing" of the capsule and was adherent to the liver, it was moderately soft. The cut surface was gray-pink in color and resembled the spleen in cases of chronic myeloid leukemia. The liver weighed 2,560 Gm and showed cloudy swelling only. The right femur showed hyperplastic gray-pink marrow throughout its entire length, as did the right tibia up to a point 2 inches (5 cm) from its distal extremity. The sternum showed similar gray-pink marrow. The lungs showed multiple pyemic abscesses and a recent infarct. The right kidney was large, weighed 410 Gm and showed extensive chronic suppuration involving almost all the kidney. There was a large amount of yellow gravel. The other kidney was normal.

Histologic Examination—*Spleen*. The pulp was largely converted into myeloid tissue, showing all stages of cell development from myeloblasts to mature, segmented polymorphonuclear leukocytes, the latter predominating. Megakaryocytes were present but were scanty. There was no lymphoid tissue left in the organ.

Bone Marrow. The bone marrow showed extensive myeloid hyperplasia, which had completely replaced the fat of the marrow. Megakaryocytes were numerous. There was no fibrosis. The marrow cells were mainly myelocytes, but there were scattered "myeloblast islands." Immature cells were more numerous than the more mature forms of the myeloid series. The condition of the marrow was consistent with that in true myeloid leukemia.

Liver. The liver showed cloudy swelling and scanty myeloid infiltration in the sinusoids. The cells were predominantly polymorphonuclear leukocytes, but occasional immature cells were also present. Megakaryocytes were not obvious. Only occasional abnormal cells were found in the portal tracts.

Lungs. The lungs showed foci of suppuration. There were large numbers of myeloid cells and numerous megakaryocytes in the capillaries.

Kidneys. Only foci of suppuration were noted in the kidneys.

Other Organs. None of the other organs showed striking changes. Most of the organs showed myeloid cells in the capillaries, but the development was

not so pronounced as in the lungs, nor were megakaryocytes demonstrable in organs other than the spleen or lungs

Postmortem Diagnosis—The diagnosis was chronic leukemia, with splenomegaly and hyperplasia of the marrow. In addition there were suppurative pyelonephritis due to calculus and terminal pyemia

CASE 2—History—A white man of 76 was admitted to the hospital after an episode of superficial sepsis of the second, third and fourth fingers of the left hand, acquired during a voyage from the Netherlands to Capetown. The local lesion was incised and soon resolved. At the same time the patient stated that he had had a little hematuria, as in addition he had fever, he was hospitalized for further investigation. Since his ship had called at Freetown, Sierra Leone, and since he had a history of malaria forty years previously, it was considered possible that he had malaria. The only other significant factor in the history was that of intermittent episodes of classic gout, which the patient had had for the past twenty years

Examination—The patient was a surprisingly young-looking man, with a highly colored complexion. There was no jaundice, clubbing of the fingers or cyanosis. There were healing ulcers on the tips of the third and fourth fingers of the left hand. No abnormalities were detected in the cardiovascular system, there was no cardiac enlargement. Blood pressure was 124 systolic and 60 diastolic. The spleen was palpable 3 fingerbreadths below the costal margin. Its surface was smooth, and it was firm, with a sharp edge. The liver was also palpable 3 fingerbreadths below the costal margin and was also firm and smooth. No abnormalities were present in the other systems. There were no palpable lymph nodes. The urine was normal. Repeated search for malaria parasites proved unsuccessful. The pyrexia gradually subsided, cause for it was never adequately established. The level of blood uric acid was 4.0 mg per hundred cubic centimeters. The blood count (tables 1 and 2) almost reached the level for polycythemia, and there was a great increase in cells of the myeloid series. The differential bone marrow count (table 3) indicated a myeloid reaction, the number of myelocytes being in the upper level of the normal range. Roentgenologic studies of long bones revealed no abnormalities

Course—The patient was transferred to the outpatient department, where he received a total of 172 r in body baths over the next three months. Three months after the roentgen therapy was completed, he had a typical episode of gout, which was no different from those he had experienced previously, and which gradually subsided

Three months later he noticed coldness and blueness of the terminal portions of the two medial toes of the right foot, he had also experienced an episode of "pins and needles" in the foot. He was readmitted to the hospital for further investigation. The spleen then extended only 1 fingerbreadth below the costal margin, and the liver was unaltered. The blood findings were also essentially the same. Local examination of both legs disclosed symptoms consistent with organic occlusion to the vessels of both feet. There was definite cyanosis of the tips of the toes, depending on room temperature, and both feet were cold. Skin temperatures were right foot, 22 to 23 C, left foot, 24 to 25 C.

The plethysmographic examination, made by Prof. R. H. Goetz, indicated that pulse volume during full dilatation was 0.005 cc (normal volume is 0.02 cc). Rate of flow was larger than one would have expected, the reduction in pulse volume indicating a relatively well developed collateral circulation. The level of

blood uric acid was 67 mg per hundred cubic centimeters. Blood pressure was 160 systolic and 90 diastolic. The patient was treated by intermittent venous occlusion and lumbar diathermy, and papaverine was administered. He improved for a while, but the local condition recurred, and he was submitted to lumbar sympathectomy. Unfortunately, severe wound sepsis due to a penicillin-resistant streptococcus developed, and the patient died about three weeks after the operation.

Autopsy (performed by Dr G Selzer)—Owing to legal delays the autopsy could not be performed until thirty-six hours after death. The organs all showed considerable postmortem change. There was atheroma of the right and the left coronary artery, the left one was completely occluded about 3 cm from the coronary orifice. The liver weighed 1,700 Gm. The kidneys were somewhat scarred, and there was gravel in both renal pelves. The spleen was greatly enlarged and weighed 755 Gm. The bone marrow was extremely hyperplastic. The whole of the femur was replaced with red marrow, as was the upper 2 inches (5 cm) of the tibia. There was, however, a diffuse overgrowth of the marrow with bony trabeculae. There were no enlarged lymph nodes.

Histologic Examination—Microscopically, none of the viscera except the spleen showed infiltration with myeloid cells. In the liver there were very scanty groups of cells in the portal tracts. The spleen showed considerable postmortem change. The lymph follicles were, however, still recognizable. There was considerable infiltration of myeloid cells, mainly polymorphonuclear leukocytes, in the splenic pulp. The condition of the bone marrow did not differ essentially from that seen during life, with the exception of the presence of osteosclerosis.

Postmortem Diagnosis—There was considerable myeloid hyperplasia in the spleen and bone marrow, associated with osteosclerosis. There was no "true leukemia."

CASE 3—History—A white man of 62 had been well until about seven years previous to examination, when he had begun to experience recurrent episodes of acute arthritis. These started in the right big toe, which was acutely tender and painful. After a month of almost continuous pain in this toe, the big toe of the left foot became involved in a similar manner. The affected joints remained swollen and painful for a further two months, at which time the disorder gradually subsided, leaving no residual joint disturbance or deformity. Several months later, the patient had further episodes of classic gout, which gradually involved more and more joints and eventually left deformity. The metatarsophalangeal joint, the carpal joints and the wrists, knees and elbows all became involved. Contributory data were not obtained from the previous history or from the family history, except for trauma of the right elbow and the left wrist years previously.

Examination—The patient had a highly colored complexion, with superficial telangiectases on the face. The mucous membranes were well colored.

Both the right elbow and the left wrist were deformed as a result of trauma. In addition, all the joints of both hands were deformed as a result of arthritis, and there was fusiform swelling of the joints of the fingers, with limitation of movement. The knees and the joints of both feet were swollen and deformed, as were the small joints of the toes. There was bursitis of the left olecranon. In addition, gouty tophi were present around the knees and the left elbow.

No cardiac enlargement was noted. The pulse was grossly irregular, due to auricular fibrillation. The vessels were arteriosclerotic. No murmurs were heard in the heart. Blood pressure was 115 systolic and 65 diastolic.

The spleen was greatly enlarged and extended about 5 inches (12.5 cm) below the costal margin. It was firm, smooth and not tender, as was the liver, which was palpable about 2 fingerbreadths below the costal margin. No other masses were palpable. The other systems were normal.

The urine was normal. The level of serum uric acid was 8.5 mg per hundred cubic centimeters. A biopsy specimen from one of the tophi showed the classic histologic features of gout. Sodium urate crystals were also demonstrated. The blood count (tables 1 and 2) almost reached the level for polycythemia. In addition, there were thrombocytosis and a gross increase in mature myeloid cells. The bone marrow (table 3) showed both myeloid and erythroid hyperplasia, with relatively scanty primitive myeloid cells.

Course—The patient responded to the usual therapy for gout and was discharged as reasonably fit. He is still alive and well at the time of writing.

Diagnosis—The diagnosis was gout associated with chronic nonleukemic myelosis.

CASE 4—History—A white woman of 64 had had malaria thirty-six years previously, with numerous recurrences for sixteen years, after which she had been free of the disease. About six years after the first episode of malaria, the spleen was found to be enlarged, the patient had been aware of a lump in the left loin for a great many years. Four years after the discovery that the spleen was enlarged, laparotomy was performed, and the diagnosis was confirmed. The patient stated that a "tumor" of the stomach was removed at the same time. Ever since the operation she had had intermittent episodes of diarrhea, lasting for one or two weeks and then clearing up for some months, only to recur. No cause for the diarrhea was found. During the episodes she passed up to ten stools per day, containing blood and mucus. For the last few years she also had had a severe dragging feeling in the left flank. One sister had polycythemia vera, and 1 brother had trouble with the "spleen" (?)

Examination—The mucous membranes were pale. The cardiovascular system was normal, blood pressure was 150 systolic and 60 diastolic. The spleen was grossly enlarged, extending to a point 4 fingerbreadths below the umbilicus. It was smooth and firm, with a sharp edge, and was slightly tender. The liver extended 3 fingerbreadths below the costal margin and was firm, smooth and not tender. The urine was normal. The blood showed anemia, a constant increase in reticulocytes and an associated increase in polymorphonuclear leukocytes. No bone marrow could be obtained, even on repeated attempts. Roentgenoscopic examination of the gastrointestinal tract and examination of the stools failed to reveal the cause of the diarrhea. The patient was discharged unimproved, she is still alive at the time of this report.

Diagnosis—The diagnosis was possible chronic hemolytic anemia as a relic of malaria. The diagnosis of osteofibrosis of bone marrow was indefinite.

CASE 5—History—A white man of 74 had had anginal pain on moderate exertion for the past ten years, as well as a feeling of tiredness and lack of energy. The symptoms had been no worse in recent years. In addition, he had episodes of what he described as a hot feeling in the body, enough to make him "want to throw the blankets away," and usually occurring about 2 a.m. The episodes were relieved by his getting out of bed. They were not associated with dyspnea.

For about eight years, the patient had had an itchy rash, covering most of the body. The rash was associated with edema of the hands and face, on one occasion the eyelids were particularly affected. The rash consisted of crops of

small, reddish papules, occurring chiefly on the arms and legs but also extending onto the body, it lasted a few weeks and then faded, being followed with desquamation. The episodes had recurred every few weeks or months. The patient also had had episodes of burning and itching of the eyes. He was admitted to the hospital because his physician had palpated an enlarged liver.

Previous History and Family History—Cholecystectomy had been performed sixteen years previously. There had been considerable indulgence in alcohol up to nine years before the hospitalization of the present report. Many members of the patient's family had "eczema." One sister died of "pernicious anemia."

Examination—The patient was a healthy-looking man with a rather florid skin. There was pronounced palmar erythema, but no rash was present. No lymph nodes were palpable.

The edge of the liver was felt 3 fingerbreadths below the costal margin. It was firm, smooth and not tender. The spleen was just felt beneath the left costal margin and was firm and smooth. No other abdominal masses were felt.

The heart was not clinically enlarged. The blood pressure was 160 systolic and 80 diastolic. The urine was normal. Results of numerous tests for liver function were within normal limits. The level of serum uric acid was 5.4 mg per hundred cubic centimeters. Roentgenograms of the chest, femurs, humeri, vertebrae and pelvis were normal and revealed no evidence of osteosclerosis. The blood showed slight anemia, with a gross increase of mature myeloid cells, however, numerous band forms were included. The bone marrow showed myeloid hyperplasia, with a slight increase in myelocytes. The patient was discharged unimproved.

Diagnosis—The diagnosis was chronic nonleukemic myelosis. The presence of chronic myeloid leukemia was not proved.

CASE 6—History—A white man of 57 had been well until about three years prior to admission to the hospital, when he began to experience recurrent headaches. These were severe, were situated on the vertex and occurred at no particular time. They were not associated with visual auras. Two years before admission, while walking, the patient had suddenly noticed a weakness in the right arm and leg, and associated difficulty with speech. The condition became worse for about twelve hours, by which time he had complete right hemiplegia and almost complete aphasia. A year elapsed before he recovered full use of the right side of the body and of speech.

Prior to admission he had had a dragging feeling in the left side of the hypochondrium. The pain was aggravated by his assuming the erect posture and relieved by his "lifting the abdomen up" with his hand. The patient had had malaria many years before, the last episode having occurred twenty-seven years previous to admission. Other family and personal history was noncontributory.

Examination—The patient's general condition was good. The lymph nodes were not enlarged. There were varicose veins in both legs, with areas of induration and pigmentation, and slight erythema of the lower parts of the legs and the dorsa of the feet, with scaly desquamation of the skin.

The liver was palpable 1 fingerbreadth below the costal margin, of normal consistency and not tender. The spleen was very large and extended down to the umbilicus. Its edge was well defined and sharp, the surface was slightly lobulated, and of firm consistency. The spleen was slightly tender. The prostate gland was soft and was not enlarged.

No cardiac enlargement was noted. The blood pressure was 170 systolic and 115 diastolic. There were residual signs of weakness of the right side of the body, and some increase in tone. The right plantar reflex was more nearly extensor.

than flexor in type, but not definitely extensor. There was no sensory loss. The urine was normal. Results of chemical analyses of the serum were: inorganic phosphorus, 3.4 mg per hundred cubic centimeters, alkaline phosphatase, 11.4 Bodansky units, acid phosphatase, 3.1 Bodansky units, uric acid, 10.2 mg per hundred cubic centimeters, thymol turbidity reaction, 4, thymol flocculation, 3, colloidal gold, 3, van den Bergh reaction, negative, there was only a minute trace of bilirubin. The level of blood urea was 37 mg per hundred cubic centimeters. Roentgenograms of long bones showed no evidence of pathologic states. The blood showed slight anemia, with a gross myeloid reaction, numerous myelocytes were present. The bone marrow, however, showed a mature type of myeloid

TABLE 1—*Erythrocytes and Thrombocytes in the Peripheral Blood in Chronic Nonleukemic Myelosis*

Case	Erythrocytes, Millions per Cu Mm	Hemoglobin, Gm per 100 Cc	Volume of Packed Cells, Percentage	Reticulocytes, Percentage	Thrombocytes, Millions per Cu Mm
1	4.97	14.7	43.0	1.8	1.5
2	5.85	16.6	55.0	1.0	0.76
3	6.50	17.8	51.5	2.4	1.7
4	3.25	8.1	23.0	5.0	0.41
5	3.94	13.3	43.0	3.0	0.197
6	3.20	13.5	39.0		0.577

TABLE 2—*White Blood Cells in the Peripheral Blood in Chronic Nonleukemic Myelosis*

Polymorphonuclear Leukocytes, %											
Case	Leuko- cytes, Total per Cu Mm	Mature Cells				Immature Cells		Total Cells	Lympho- cytes, %	Mono- cytes, %	Red Cell Series, %
		Neutro- phils	Eosino- phils	Baso- phils	Band Forms	Myelo- cytes	Myelo- blasts				
1	33,400	90.0	2.0	0	0	1.0	0	93.0	5.0	2.0	1.0
2	26,000	63.0	0	0	0	18.0*	0	81.0	19.0	0	0
3	24,000	80.0	4.5	1.5	4.0	0	0	90.0	10.0	0	0
4	14,000	78.0	0	0		0	0	78.0	16.0	6.0	0
5	44,250	71.5	2.75	2.75	15.0	5.0	0	97.0	2.0	1.0	3.0
6	93,550	52.5	0	2.0	21.0	19.0	0	94.5	5.0	0.5	1.0

* The cells in this case, which were not classic myelocytes, resembled monocytes in many respects.

hyperplasia, with relatively scanty myelocytes and more primitive cells. The patient was discharged unimproved.

Diagnosis—The diagnosis was chronic nonleukemic myelosis. The diagnosis of chronic myeloid leukemia was indefinite.

STUDIES OF BONE MARROW SECTIONS

CASE 1—The marrow was studied by others during life and reported as non-leukemic. At autopsy, the marrow was consistent with leukemic marrow.

CASE 2—Gross nonleukemic myeloid hyperplasia was demonstrated during life in sections made from aspirated sternal marrow. Active marrow was also obtained from the femur during life (Merskey¹⁹). No osteosclerosis or osteofibrosis was demonstrated in the sections obtained during life. At autopsy, however, pronounced overgrowth of the marrow with bone trabeculae was demonstrated.

CASE 3—Gross nonleukemic myeloid hyperplasia was demonstrated during life in sections made from aspirated sternal marrow. No osteosclerosis or osteofibrosis was demonstrated in the sections.

CASE 4—No marrow was obtained, even after repeated attempts, it was possibly fibrotic. Trephinement was not attempted.

CASES 5 AND 6—Mild nonleukemic myeloid hyperplasia was demonstrated during life in sections of aspirated sternal marrow, "hyperplasia in extension"¹⁹ was shown in specimens of the marrow of the femur. The sternal marrow in these 2 cases did not seem to be so grossly hyperplastic as that in the first 3 cases.

Megakarocytes were numerous in all cases.

TABLE 3—*Differential Bone Marrow Counts in Chronic Nonleukemic Myelosis*

	Cases			
	2	3	5	6
	White Blood Cell Series, %			
Myeloblasts	1.0	0.66	0.25	0.75
Premyelocytes	1.0	1.33	2.25	1.75
Myelocytes	29.0*	10.0	16.25	8.50
Metamyelocytes	5.0	10.0	18.5	11.5
Eosinophilic myelocytes	0	0.33	0.75	0
Band forms	18.0	16.0	9.75	22.25
Polymorphonuclear leukocytes				
Neutrophils	40.0	29.0	42.25	49.0
Eosinophils	1.0	0.33	0.75	0
Basophils	0	0.33	0.75	0.5
Lymphocytes	2.0	6.0	5.25	3.0
Monocytes	0	0.66	0	0.5
	Red Blood Cell Series, %			
Erythroblasts	0	1.0	0	0.25
Late erythroblasts	1.0	12.66	0	1.0
Normoblasts	2.0	11.66	3.25	1.0
Myeloid-erythroid ratio	31.7:1	2.83:1	28.2:1	41.8:1

* The cells in this case, which were not classic myelocytes, resembled monocytes in many respects.

COMMENT

Clinical Picture—There was nothing particularly characteristic about the clinical picture. All the patients were elderly, and in all cases the disease followed a somewhat symptomless course. The chief symptoms were of a general nature, such as vague feelings of ill health and lack of strength. A feeling of a heavy weight in the left loin was commonly encountered. Usually the general symptoms were related to the degree of anemia. A previous history of malaria was encountered in 3 of the 6 cases, but in all cases the last episode had occurred at least twenty years prior to examination. It was impossible to assess the importance of this factor, but it seemed to be relatively minor. Certainly there was no evidence of active malaria. With the exception of gout, all the other symptoms could have been fortuitous in patients of such an age, as they were mainly cardiovascular in nature. The association

of gout with this clinical syndrome is interesting. It has long been realized that there is an association between gout and leukemia (Vining and Thomson, Forkner, Lambie²⁰), between gout and remissions of pernicious anemia induced by the administration of liver, even when the liver extract used is purine free (Riddle, Opsahl, Morlock and Rosenberg²¹), between gout and types of hemolytic anemia (Lambie^{20c}), and between gout and polycythemia vera (Isaacs, Davis, Weber, Tinney and others²²). It has been generally assumed that the hyperuricemia is due to excessive maturation of the normoblasts or of the leukocytes in the bone marrow. It appears to be related to excessive production of either red or white cells in the bone marrow. Nevertheless, the relation is by no means a constant one, Lambie^{20c} suggested that the role of heredity may be of importance in predisposition to the disease. However, in the cases reported in this paper in which gout was associated, there was no history of a familial predisposition. The case reported by Reifenstein²³ as "Erythremia, Gout and Subleukemic Myelosis" appears to parallel the case in this series very closely. There was no real reason to classify the case as one of erythremia, as the evidence for plethora was not satisfactory.

Blood—In 2 cases the red cell count was normal. A mild degree of anemia was present in 1 case and severe anemia, in another case, whereas in 2 cases the count almost reached the level for polycythemia. However, as I have stated elsewhere,²⁴ the counts were just below diagnostic levels for polycythemia. The number of reticulocytes was normal in 3 cases, just above normal in 1 case and consistently raised in another case. The high count raised the possibility that the last case was one of chronic hemolytic anemia, possibly a relic of past malaria, which is one of the known causes of the syndrome. Erythrocyte fragility to hypotonic saline solution was normal in this case, and sickling of the red cells could not be demonstrated. The number of thrombocytes was

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23 Reifenstein, G H. *Am J M Sc* **197** 215, 1939, *ibid*, **210** 638, 1945.

24 Merskey, C. To be published.

within the normal range in 4 cases, but in 2 it was 1,500,000 and more per cubic millimeter. In 1 of the latter cases the red cells approximated the level for polycythemia, an increase was thus shown in all the cell elements of the peripheral blood, that is, the red cells, the white cells and the thrombocytes. The white cells were increased in all cases and showed varying degrees of immaturity, associated in 2 of the cases with immaturity of the red cells as well. In none of the cases were myeloblasts present in the peripheral blood, but in all, the cells of the polymorphonuclear leukocyte series were grossly increased, both relatively and numerically. There were, however, no constant correlations between the increases in the red cell series, in the white cell series and in the thrombocytes.

Bone Marrow—There was no doubt of the hyperplasia of the bone marrow in these cases. Hyperplasia was present *in situ* as well as in extension. Autopsy material demonstrating the hyperplasia was available in 2 cases (cases 1 and 2). In cases 3, 5 and 6, hyperplasia *in situ* was shown in sections of bone marrow taken during life, in cases 5 and 6, hyperplasia in extension was shown in biopsy specimens taken simultaneously from the marrow of the femur.

Curiously enough, in the 2 cases which came to autopsy the extent of the hyperplasia of the marrow was limited and did not occupy the whole length of the tibia. In 1 case it extended to within 2 inches (5 cm) of its distal extremity, and in the other case it only involved the upper 2 inches of the bone.

Marrow specimens for microscopic study were available in 5 cases. In case 1, results of two examinations of the marrow made during life had been interpreted as not inconsistent with normal marrow, yet, the final conclusion at autopsy was that the marrow was, in fact, leukemic. One of the reasons for the error lay in the fact that the examinations of the marrow during life had been made only on smear preparations, no sections had been prepared from the aspirated marrow particles.¹⁹ Thus, the hyperplasia had been missed. Furthermore, the increase noted in the less mature cells was relatively scanty, even at autopsy, and as the examinations had been carried out several years before death, there may have been an alteration in the marrow picture. Unfortunately, the patient refused a third puncture of the marrow, and the original smears were not available for study.

Adequate marrow sections and smears were available in case 2. In the smears of peripheral blood and of the marrow in this case, there were many atypical cells, which have been classified in the tables as myelocytes, but which were certainly not typical myelocytes. They resembled monocytes in that they had the lobulated, "folded over" nucleus of those cells. There were, however, apparent gradations

between these cells and typical myelocytes. In the marrow there was gross hyperplasia of the myeloid series, as well as osteosclerosis. A curious fact is that hyperplasia of the marrow did not extend to the rest of the tibia. The differential count of the marrow cells in this case demonstrated very little immaturity of the cells, nor did the viscera show infiltration with myeloid cells. Even in the spleen, where there was considerable reaction, the lymph follicles were still preserved.

In cases 3, 5 and 6, the hyperplasia of the marrow was pronounced, but in none of these cases was there much increase in the number of immature cells in the marrow.

The red cell series was practically absent in cases 1, 2, 5 and 6. Despite this fact, it will be noted that the red cell count in case 2 could easily be described as polycythemic. In case 3, in which the red cell count was also high, there were numerous cells of the red cell series in the bone marrow.

Diagnosis—This rather mixed collection of cases includes 1 case of true chronic myeloid leukemia, 1 case of osteosclerosis with myeloid reaction, 1 case of possible chronic hemolytic anemia (or myelofibrosis) and 3 cases of (possibly) "nonleukemic" myelosis. It was not possible to make a diagnosis during life in the case of osteosclerosis, despite roentgenologic examination of the bones and biopsy of aspirated marrow sections. The diagnosis could perhaps have been made from a section of the sternal marrow obtained by trephination. Chronic hemolytic anemia can usually be diagnosed, but in case 4 the only evidence pointing to that disease was the consistently elevated reticulocyte count. The failure to obtain bone marrow on repeated puncture could perhaps be interpreted as evidence of fibrosis of the marrow, the patient refused to allow trephination to obtain a specimen of the marrow. The real difficulty in diagnosis lay in the differentiation of these disorders from true chronic myeloid leukemia. This factor raised the extremely difficult problem of exactly what is required for a diagnosis of chronic myeloid leukemia. Acute leukemia is usually easy to diagnose, as the examination of the marrow discloses great numbers of immature cells. In less acute cases, however, there are fewer myeloblasts and more myelocytes, in the chronic stages, the cells may become even more mature. It is not possible to lay down exact criteria for diagnosis, to say how many immature cells must be present or how immature the cells must be. Piney and Hamilton-Paterson,²⁵ for instance, stated that the increase in the cellularity of the marrow in the ordinary chronic stage of the disease depends almost entirely on the increase in the number of myelocytes, which may form as much as

²⁵ Piney, A., and Hamilton-Paterson, J. L. *Sternal Puncture*, ed. 3, London, William Heinemann, Ltd., 1946.

80 per cent of the white cells, a greater increase among cells less differentiated than myelocytes is an indication either of a relapse or that the disease is passing into an acute phase. These authors also stressed the aggregation of cells of a single cell type, such as myelocytes, premyelocytes or myeloblasts. This characteristic, however, can be seen only in thick smears or, better still, in marrow sections, which may be made from the aspirated sternal marrow and which also demonstrate hyperplasia of marrow *in situ*. The hyperplasia in extension may, in addition, be shown by the technic of biopsy of the marrow of the femur.

In the cases described in this series, there was hyperplasia of the myeloid cells both *in situ* and in extension, and aggregations of these cells into groups of a single cell type, yet, there was no true increase in the percentage of immature cells, as judged by generally accepted "normal" standards. Thus, even with all diagnostic aids one may fail to reach a final diagnosis, and even at autopsy the problem may remain unsolved. Some authors stress the finding of leukemic infiltrations outside the bone marrow as necessary for a proved postmortem diagnosis of chronic myeloid leukemia. The spleen is usually involved, and the remaining viscera usually show cellular infiltration. In the liver, for instance, the infiltrations are usually in the portal fields and not confined to the sinusoids. Judged by these criteria, case 1 would hardly pass for one of chronic myeloid leukemia, it should be classified as one of chronic nonleukemic myelosis, yet, the marrow was definitely leukemic.

The cases of chronic nonleukemic myelosis resemble those of chronic myeloid leukemia in many respects. There was considerable increase in the number of leukocytes, some of which were usually immature, there was hyperplasia of the leukopoietic tissue, there was often an increase in the number of thrombocytes or even of red cells, though there was oftener a normal or lowered red cell count. The great increase and immaturity in the white cells characteristic of true leukemia were usually absent, as were gross leukemic infiltrations at autopsy. Nevertheless, as Heller, Lewisohn and Palin²⁶ pointed out, the differences are really only in degree and all the differentiating features may be present in greater or lesser degree, or absent in individual cases. The greater the incidence of leukemic features, the worse the prognosis and the greater the disability. The more the condition resembles nonleukemic myelosis, the more chronic the disease and the better the prognosis. In all the cases reported in this series the disease was chronic in nature. In 5, anemia was either absent or mild in degree, and the disorder in the sixth case may well have been of a differ-

²⁶ Heller, E. L., Lewisohn, M. G., and Palin, W. E. *Am J Path* **23** 327, 1947.

ent etiology In none of the cases were myeloblasts found in the peripheral blood, even myelocytes were scanty in 4 cases The total white cell count showed all grades of increase but in general was less than that characteristic of chronic myeloid leukemia Immature red cells were found only in small numbers in the peripheral blood

I have discussed elsewhere²⁴ the true relation between myeloid leukemia and polycythemia vera and concluded that there was a relation through this intermediary group of conditions The cases reported in this paper lend further evidence to this thesis Fundamentally all the conditions are related, and they would appear to represent varying degrees of hyperplasia of the hemocytoblast, or whatever one wishes to call the precursory cell of the red cell and white cell series Should the hyperplasia involve mainly the red cell series, the clinical syndrome of polycythemia vera would result, though even in this disorder considerable proliferation of both the white cell series and the thrombocytes occurs Should the white cell series be mainly involved with minor degrees of immaturity, chronic nonleukemic myelosis would result, should the degree of immaturity be greater, the condition would be leukemia Even conditions affecting mainly thrombocytes have been reported²⁷, red cells and polymorphonuclear leukocytes were also increased in these conditions If one cares to go further back, one may say that all the cell types involved, the hemocytoblast, the megakaryocyte, the fibroblast and the osteoblast, were derived from the same primitive mesenchymal reticulum cell of Maximow, the association of all these conditions would then be easy to understand The start of the hyperplasia is more difficult of explanation, as the stimulus which initiates it is not known¹⁸ Nevertheless, this hypothesis makes the relation of these diseases easy to understand

SUMMARY AND CONCLUSIONS

The condition known as chronic nonleukemic myelosis is discussed, and cases of this syndrome are reported The essential feature of the condition is hyperplasia of the leukopoietic tissues of the body, which results in an increase in the white cell count and in a degree of immaturity in the white cells of the peripheral blood The bone marrow, especially, shows gross overgrowth of cells of the myeloid series In addition, varying amounts of myeloid infiltration may be found in other organs, though the degree tends to be slight Even in the marrow, the hyperplasia appears relatively orderly in nature Consequently, the marrow does not display the invasive characteristics seen in true leukemia The course of the condition is prolonged, anemia tends to be slight,

²⁷ Rowlands, R. A., and Vaitzev, I. M. *Lancet* 2 1217 (1938) Reid, J. *ibid* 2 584 (1940)

and disability is often negligible for some years. The bone marrow is not leukemic, in that it does not show immaturity at the myeloblast level, which is characteristic of true leukemia, nor need myelocytes even be very numerous. Nevertheless, the condition may be only a mild variant of leukemia differing only in degree, rather than in any fundamental characteristic.

A similar clinical syndrome may be encountered in myelofibrosis, osteosclerosis, carcinomatosis of bone, myelomatosis or chronic hemolytic anemia. The differential diagnosis may be impossible during life.

The syndrome is also related to polycythemia vera and forms a connecting link between polycythemia vera and true leukemia. It is possible that the syndromes of polycythemia vera, nonleukemic myelosis and true leukemia, and even, possibly, osteosclerosis and myelofibrosis, have a common genesis.

This work was carried out in the department of Prof J F Brock, Miss J M Lardner, B Sc, and Miss P M Hofmeyr, B Sc, gave technical assistance, Prof B J Ryrie, Prof M Van den Ende, Dr G Selzer and the staff of the Pathology Department, University of Capetown, gave assistance with the autopsy material and the bone marrow sections and Prof F Forman and Prof J F Brock gave permission to use reports of some of their cases.

CHRONIC ULCERATIVE COLITIS AND CARCINOMA

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THE PURPOSE of this communication is to present data on a series of 855 cases of chronic ulcerative colitis, with specific reference to the development of pseudopolyposis and carcinoma

A review of the literature appears to indicate a growing conviction that carcinoma may develop in patients with chronic ulcerative colitis and pseudopolyposis of long standing. The inference is that the malignant process occurs in the pseudopolyps and in association with, or as the result of, the existing chronic intestinal infection. The reported incidence of such malignant growths varies with different authors. Streicher (1938)¹ reported 12 per cent of 217 cases. Matzner and Schaefer (1939)² found the incidence of carcinoma among 185 patients with chronic ulcerative colitis to be 16 per cent, as compared with 0.5 per cent of the general hospital admissions. Brust and Bargaen,³ in 1934, reported an incidence of 2.5 per cent of 800 cases. In a study of necropsy and biopsy material, they noted transitional phases from chronic ulcerative colitis with pseudopolyposis to adenoma or carcinoma. The next year, Hurst⁴ reported polyposis occurring as a complication in 12.5 per cent of 40 patients with chronic ulcerative colitis. Independently of this group, he noted 3 cases of carcinoma, the malignant process in 1 instance developing three years after the patient had completely recovered from ulcerative colitis. Jackman, Bargaen and Helmholtz⁵ reported carcinoma of the colon in 63 per cent of a series of 95 children, as compared with 32 per cent in an over-all

From the Dysentery Registry

1 Streicher, M. H. Clinical Course of Chronic Ulcerative Colitis, *Am J Digest Dis* **5** 361 (Aug) 1938

2 Matzner, M. J., and Schaefer, G. Chronic Ulcerative Colitis Complicated by Carcinoma, *Rev Gastroenterol* **6** 422 (Sept-Oct) 1939

3 Brust, J. C., and Bargaen, J. A. The Neoplastic Factor in Chronic Ulcerative Colitis, *New England J Med* **210** 692 (March 29) 1934

4 Hurst, A. F. Prognosis of Ulcerative Colitis, *Lancet* **2** 1194 (Nov 23) 1935

5 Jackman, R. J., Bargaen, J. A., and Helmholtz, H. F. Life Histories of Ninety-Five Children with Chronic Ulcerative Colitis. Statistical Study Based on Comparison with Whole Group of Eight Hundred and Seventy-One Patients, *Am J Dis Child* **59** 459 (March) 1940

group of 871 patients with chronic ulcerative colitis. In 1944, Cattell⁶ noted intestinal carcinoma in 11 patients with chronic ulcerative colitis of five years' duration or longer. Bargaen and Sauer⁷ reported 30 additional cases the same year, making a total of 44. Seventeen of the 30 patients had multiple polyps and 9 multiple carcinoma. In a previous study (1929), polyposis had been noted in 10 per cent, and carcinoma in 2.5 per cent, of 693 patients. Ricketts, Benditt and Palmer,⁸ in 1945, described carcinoma of the descending colon arising in an area of chronic ulcerative colitis. The patient in this case was 18 years old and had had colitis for fifteen and a half years. The terminal portion of the ileum was also affected. Cattell and Boehme,⁹ during a period of seven years, encountered 9 patients with chronic ulcerative colitis and carcinoma, the average duration of the colitis being nine years. In 1946, Ricketts and Palmer¹⁰ reviewed 206 cases of chronic ulcerative colitis. Pseudopolyposis was present in 21 (10 per cent), and carcinoma occurred in 1.4 per cent. Kirsner, Palmer, Maimon and Ricketts¹¹ recently described 2 cases of carcinoma in a selected group of 100 cases of ulcerative colitis. In a review of 630 cases of chronic ulcerative colitis at the Lahey Clinic during the period from 1927 to 1946, Cattell and Sachs¹² reported that 166 patients (26 per cent) were operated on, of these, 7 per cent exhibited carcinoma. The average duration of colitis in the patients with carcinoma was nine years.

For clarification of the problem of the development of carcinoma from pseudopolyposis in chronic ulcerative colitis, a definition of terms appears advisable. This is particularly true because, both in the literature and in medical practice, there is considerable confusion as to the etiology, pathology, differentiation and treatment of intestinal polyps. Any localized projection of tissue, sessile or pedunculated, may be regarded as a polyp. In the intestine the lesion generally arises from the mucosa and projects into the lumen of the bowel. It may, however,

6 Cattell, R. B. Indications for Colectomy, *S. Clin. North America* **24** 656 (June) 1944.

7 Bargaen, J. A., and Sauer, W. G. The Association of Chronic Ulcerative Colitis and Carcinoma, *Clinics* **3** 516 (Oct.) 1944.

8 Ricketts, W. E., Benditt, C. P., and Palmer, W. L. Chronic Colitis with Infantilism and Carcinoma of Colon, *Gastroenterology* **5** 272 (Oct.) 1945.

9 Cattell, R. B., and Boehme, E. J. Chronic Colitis Complicated by Carcinoma of Colon and Rectum, *S. Clin. North America* **26** 641 (June) 1946.

10 Ricketts, W. E., and Palmer, W. L. Complications of Chronic Nonspecific Colitis, *Gastroenterology* **7** 55 (July) 1946.

11 Kirsner, J. B., Palmer, W. L., Maimon, S. N., and Ricketts, W. E. Clinical Course of Chronic Nonspecific Ulcerative Colitis, *J. A. M. A.* **137** 922 (July 10) 1948.

12 Cattell, R. B., and Sachs, E., Jr. Surgical Treatment of Ulcerative Colitis, *J. A. M. A.* **137** 929 (July 10) 1948.

arise in the deeper portions of the wall, grow toward the lumen and push mucosa ahead of it. Two examples are the lipomatous polyp of the submucosa and the leiomyoma of the muscularis. The polyps with which the present report is concerned are those arising from the mucosa. They are of two varieties—the inflammatory polyp and the neoplastic polyp. The former is associated with chronic ulcerative colitis, is inflammatory in origin and represents pinched-off bits of intact mucosa, between areas of geographic or linear ulceration. This is the only



Fig 1—Low power photomicrograph of pseudopolyp. Note cystic glands, some lined with atrophic epithelium and others with columnar and goblet cells.

mucosa from which regeneration of epithelium can occur to cover denuded areas. These pseudopolyps vary considerably in size and shape and are usually smooth and sessile. They are almost invariably edematous, giving the appearance of lusterless, skinned grapes. Microscopically, the covering epithelium may be intact, or partly so, the underlying tissue is infiltrated with polymorphonuclear, plasma and round cells. Often the epithelium lining the crypts of Lieberkuhn is distorted or displaced, so that the normal topography is destroyed. The lining cells are normal, there is no penetration of the basement membrane, and

goblet cells carry on their normal activity (fig 1) If access of their secretion to the lumen of the bowel is prevented by closure of the mouths of the glands or ducts, cystic changes occur, with retention of mucus

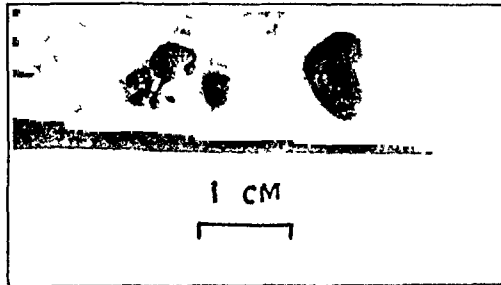


Fig 2—Pseudopolyps passed by rectum in a case of chronic ulcerative colitis



Fig 3—Low power photomicrograph of pseudopolyp Note distorted glands and intact solitary acuminate lymph nodule

The epithelium may atrophy This process, with the associated edema, gives rise to the polyps of chronic ulcerative colitis (pseudopolyposis cystica of Virchow) When the neck of the polyp is narrow or poorly

vascularized, the polyp may necrose and slough or undergo torsion and be passed with the intestinal contents (fig 2) We have never noted active proliferation of epithelium in pseudopolyps to the point of neoplasia We have repeatedly seen active extension of the epithelium to cover ulcerated areas, just as, if some lymphoid tissue remains, regeneration of solitary lymph nodules occurs Indeed, not only does fresh, pearly epithelium cover the ulcerated areas during the healing phase of chronic

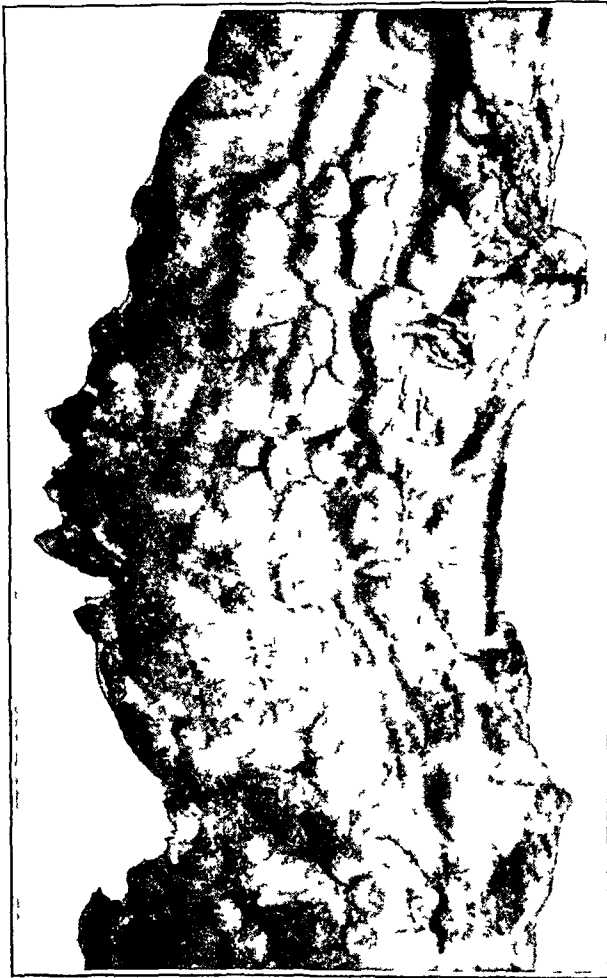


Fig 4—Pseudopolyposis in chronic ulcerative colitis Note smooth polyps between areas of linear and geographic ulceration (Felsen, J Acute and Chronic Bacillary Dysentery, *Am J Path* 12 395 [May] 1936)

ulcerative colitis, but in time the pseudopolyps may flatten out, ultimately appearing as normal mucosa We have seen this phenomenon in many patients who have repeatedly been examined for a number of years It has been our impression that inflammatory polyposis at one time or another is a rather constant phenomenon in cases of chronic colitis with extensive ulceration At one stage, biopsy may actually reveal intact solitary acuminate lymph nodules within a polyp (fig 3) We have never noted gross or microscopic evidence of malignancy in polyps due

to chronic ulcerative colitis Swinton and Warren,¹³ in a study of the histopathology of a large series of intestines of patients with chronic ulcerative colitis, did not detect evidence of malignancy in any polyp. It may be of interest that the inflammatory polyposis present in the colon often extends into the ileum (figs 4 and 5). Yet, to our knowledge, the proponents of malignancy due to pseudopolyposis have never noted such malignancy in the ileum. If their concept is correct, there is

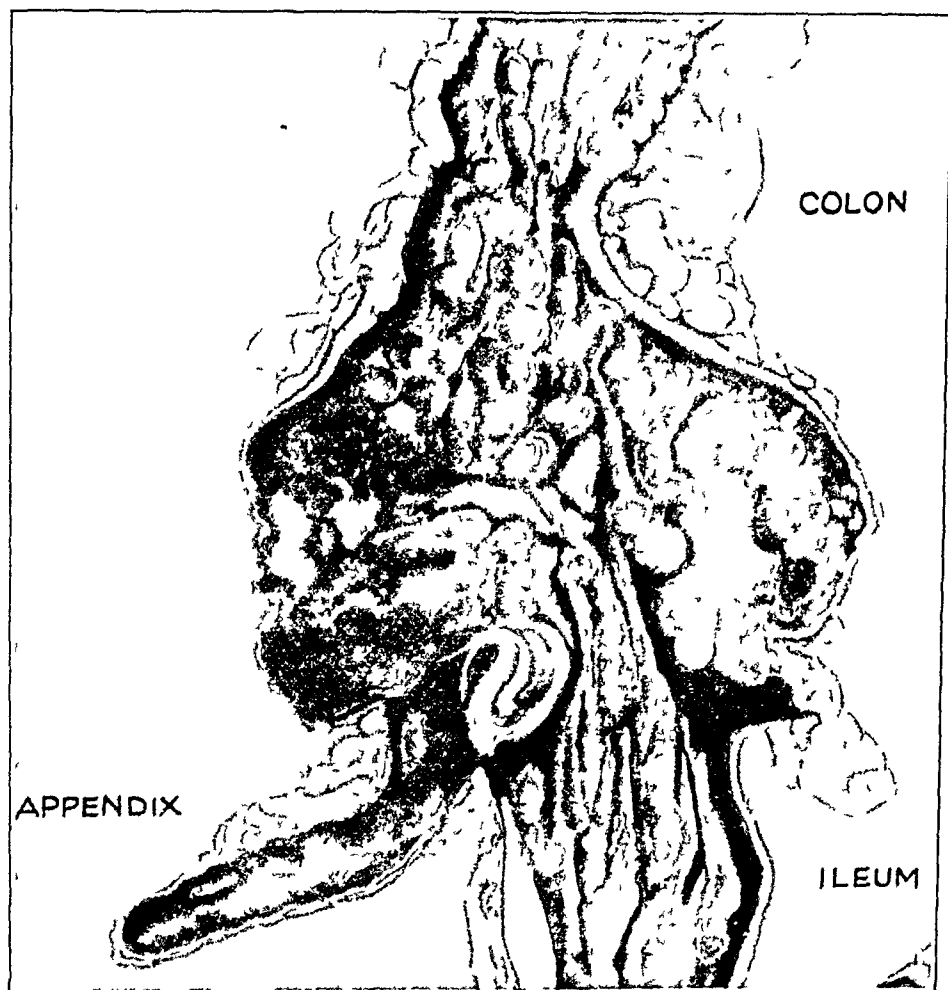


Fig 5—Pseudopolyposis in chronic ulcerative colitis involving colon, appendix and ileum (Felsen, J. Bacillary Dysentery, Colitis and Enteritis, Philadelphia, W B Saunders Co, 1945)

no reason that the ileum should not be involved, since the pathologic condition of pseudopolyposis would be identical with that in the colon. Primary adenocarcinoma of the ileum is rare, but it does occur. We have seen at least 1 instance, in a patient without any other pathologic lesions of the intestine.

13 Swinton, N W, and Warren, S. Polyps of the Colon and Rectum and Their Relation to Malignancy, *J A M A* **113** 1927 (Nov 25) 1939

In an attempt to determine a basis for the occurrence of carcinoma in patients with pseudopolyposis, we have found it necessary to consider the possibility of the development of malignancy as an independent phenomenon, entirely unrelated to chronic ulcerative colitis. In considering the second type of mucosal polyp—the adenoma—we shall omit, for obvious reasons, the condition known as adenomatosis coli, in which the entire colon, and rarely the stomach and small intestine, is studded with innumerable adenomas. The intervening mucosa is normal, the condition involves a hereditary factor of the mendelian type, usually affects several members of a family and is prone to multicentric malig-

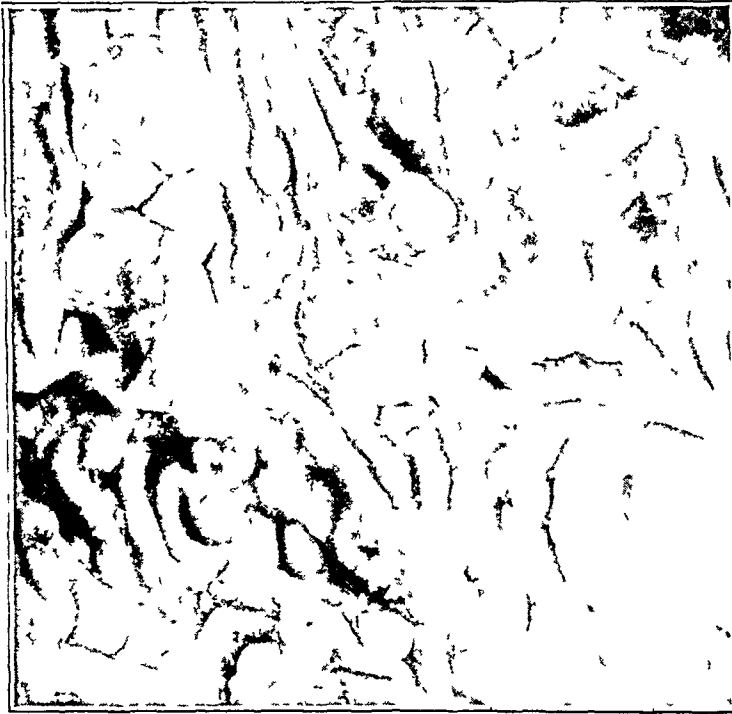


Fig 6—Neoplastic polyps (adenomas) in varying stages of development, from a small sessile type to pedunculated forms. Note delicate lobulation, in contrast to smooth surface of inflammatory pseudopolyp (fig 4)

nant degeneration. It is of relatively infrequent occurrence. This is not the case, however, with widely separated adenomatous polyps, one or more of which are frequently found in the colon. In a series of 955 necropsies on persons of various ages, at the Bronx Hospital, the incidence of two or more adenomatous polyps in the colon was 6.4 per cent. When the newborn are excluded, the incidence was 9.6 per cent. These figures are for patients without ulcerative colitis. They represent a fair cross section of the population in the area in which our patients with ulcerative colitis live. It is reasonable to assume that adenomatous polyps occur in patients with chronic ulcerative colitis at a rate similar to that for patients without the disease. The incidence of carcinoma of the colon

among 12,025 patients admitted to the Bronx Hospital in 1946 and 1947 was 99, or 0.8 per cent (this figure excludes the newborn)

The growth of adenomatous polyps has been traced from small, sessile, localized areas of glandular hyperplasia, scarcely visible to the naked eye, to the large, reddish, delicately lobulated, solid masses, like mushrooms at the end of a pedicle of mucosa (figs 6, 7 and 8). The pedicle is generally broad at the base, where it is continuous with normal mucosa, and somewhat tapering near the top, where it joins the tumor

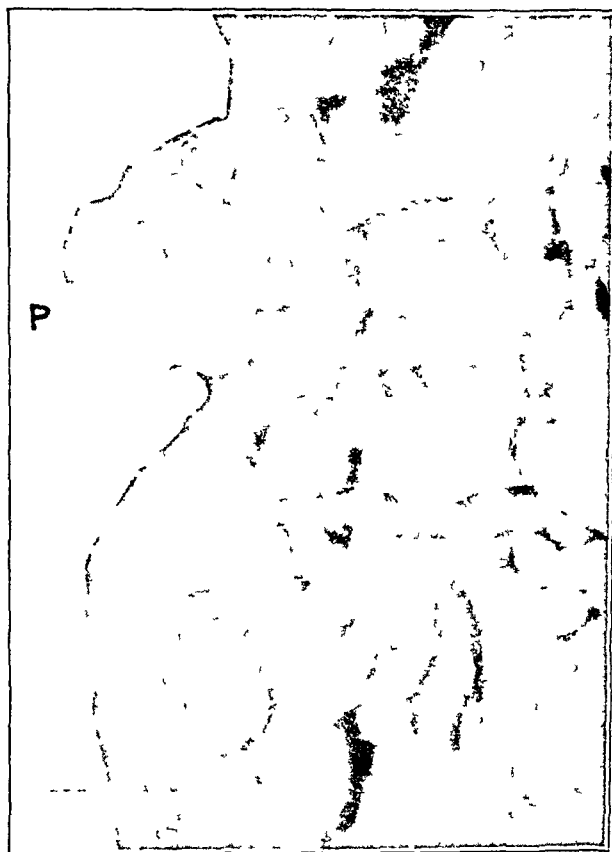


Fig 7—Adenoma (P) with long pedicle, at the base of which is a sessile adenoma

These pedicles, at least the longer ones, merely represent normal mucosa, which has been drawn away from its loose attachment to the submucosa when the intestine attempted to rid itself of the tumor, as it would a foreign body. In some instances traction on the mucosa by the dead weight of the tumor appears to have been responsible for formation of the pedicle. The latter may carry with it some submucosa, and occasionally the muscularis and serosa as well (fig 9). When the serosa is drawn up into the base of the pedicle, there is danger of opening the peritoneal cavity in snaring the polyp.

It is rather generally accepted that adenomatous polyps form the basis for many carcinomas of the large bowel. This does not imply that all adenomas tend to become malignant. When malignancy supervenes, a previously pedunculated tumor tends to become sessile and to grow, both toward the lumen of the bowel and intramurally to the submucosal lymphatic plexus, which may act as a formidable barrier for some time. Eventually the neoplastic process breaks through to involve the lymphatics of the inner (circular) muscularis, the intermuscular lymphatics, those of the outer (longitudinal) muscularis and, finally, the serosa and

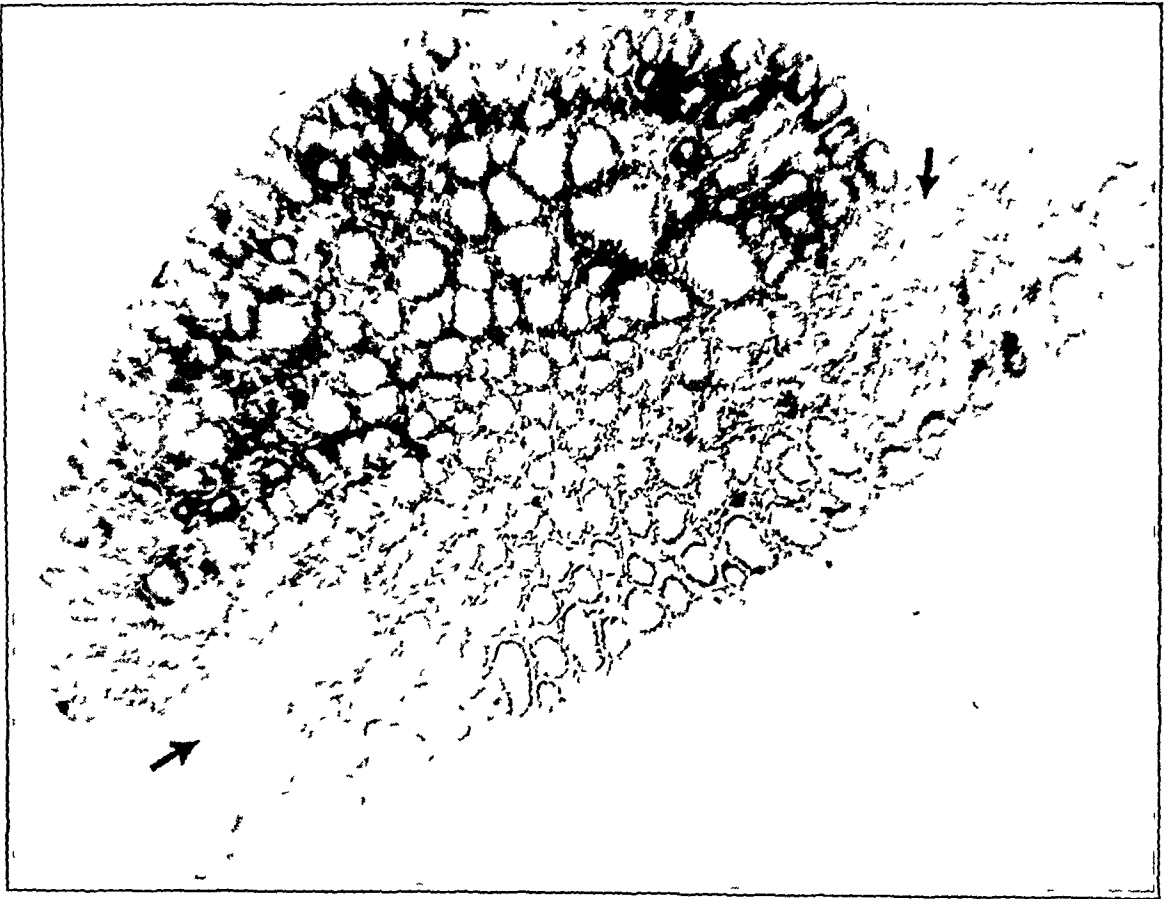


Fig 8—Low power photomicrograph of small pedunculated adenoma. Arrows indicate short pedicle.

extraserosal lymph nodes (fig 9). The neoplastic glands are disposed in the general direction of the involved lymphatics (circular or longitudinal). Intramural spread is fan shaped, so that a relatively small malignant adenoma or adenoma destruens on the mucosal surface appears as a much larger tumor on the serosal aspect.

Pseudopolyposis is inflammatory in origin and associated with active infection, as evidenced by ulceration and intramural cellular infiltration. Adenomatous polyps exhibit none of these characteristics. No acceptable

evidence has been presented with respect to their origin. Vague statements regarding "chronic irritation" and infection have often been presented, but all that is really known at present is that adenomatous polyps represent an autonomous new growth of tissue. The pseudopolyposis of chronic ulcerative colitis is merely a polypoid form of mucosa which has survived a process of necrosis associated with inflammation. Our studies indicate that sufficient active proliferation of epithelium

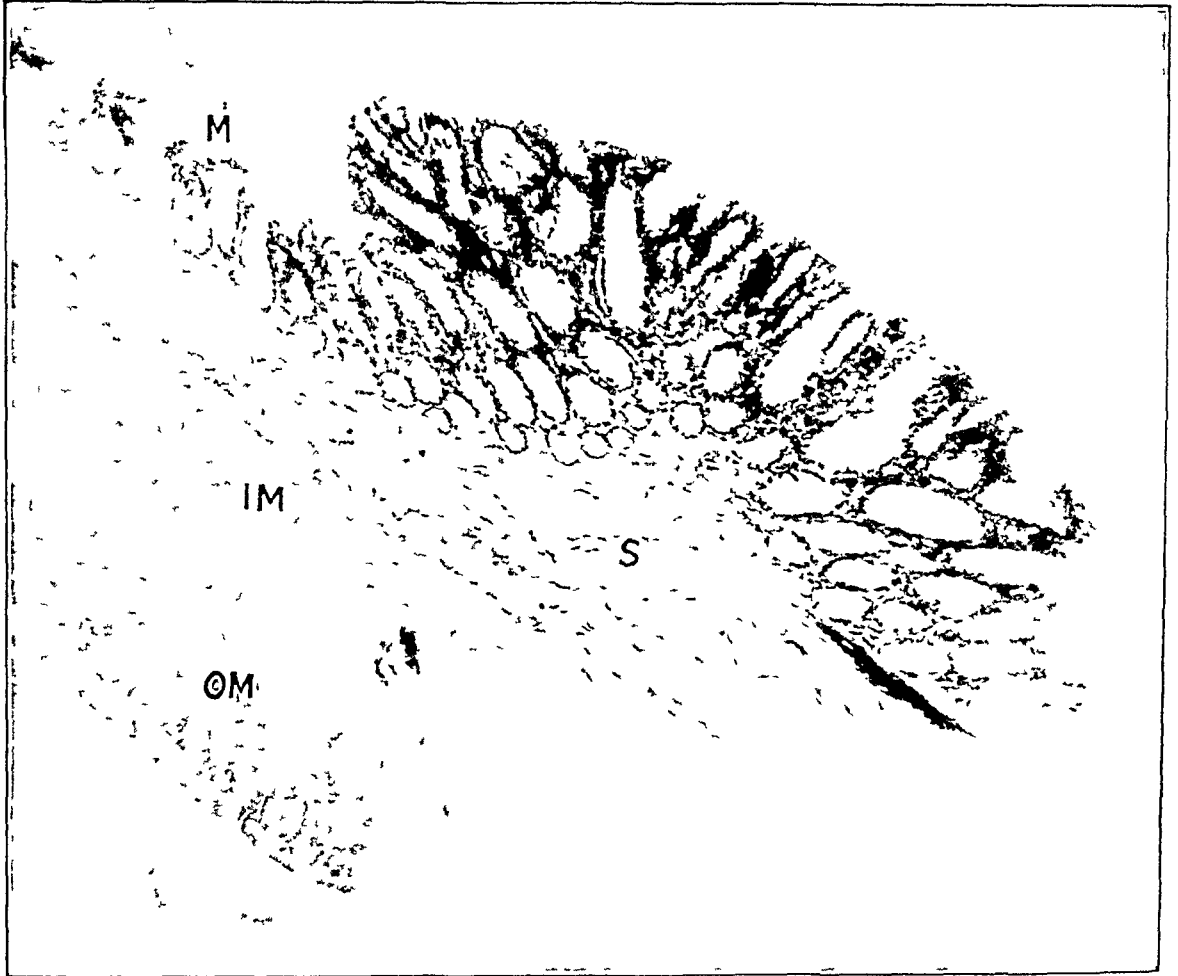


Fig 9—Photograph of small sessile adenoma (higher power than figure 8). Some submucosa (*S*) is being drawn up into the base. *M* indicates mucosa, *IM*, inner (circular) muscularis, *OM*, outer (longitudinal) muscularis.

occurs during the healing phase to cover adjacent denuded areas, but in our experience the process has never progressed to a stage that could be interpreted as neoplasia. The end result is a smooth, flat mucosa, not a tumor. We have occasionally noted one or more adenomas in cases of chronic ulcerative colitis. The incidence, however, is well below that in our control group referred to previously.

CLINICAL DATA

A statistical analysis of 855 cases of ulcerative colitis follows. All patients were examined repeatedly over considerable periods, 134 (15.7 per cent) exhibited polyposis. In the published reports on the development of carcinoma in polyposis, two striking features appear. One is the development of a malignant growth in young persons with polyposis, the other is the frequent development of a malignant growth in those

TABLE 1—*Distribution of Polyposis According to Age in 134 Cases*

Age, Years	Number of Cases	Percentage
0-9	2	1.0
10-19	7	6.0
20-29	34	25.0
30-39	35	26.0
40-49	35	26.0
50-59	16	12.0
60-69	5	4.0

TABLE 2—*Distribution of Polyposis According to Duration of the Disease in 134 Cases*

Duration, Years	Number of Cases	Percentage
1-4	60	44.8
5-26	74	55.2

TABLE 3—*Duration of Polyposis According to Selected Age Groups (98 Cases)*

Age, Years	Number of Cases of Polyposis	
	Five Years or More	Nine Years or More
20-29	21	8
30-39	16	11
40-49	23	11
50-59	0	8
Totals	60	38

patients who have had chronic ulcerative colitis for a long time (five years or more and nine years or more, in different studies). We have therefore analyzed our figures from the standpoint of these two factors.

The youngest patient was 20 months old and the oldest 67 years. Fifty per cent of patients were in the 20 to 39 year age groups and 42 per cent in the 40 to 69 year age groups.

Seventy-four patients (55.2 per cent) had had the disease five years or longer, and 38 patients (28.3 per cent), nine years or longer. The extremes of duration in the series of 134 patients were two months and twenty-six years.

None of the 134 patients with polyposis exhibited a malignant tumor in spite of a fairly even distribution, both as to age groups and long duration. None of the entire group of 855 patients with chronic ulcerative colitis has shown evidence of a malignant growth at the time of this report, although the majority have had the disease for many years and have been repeatedly examined during this period. It is reasonable to assume that even had we missed a diagnosis of malignant growth initially, the subsequent follow-up examinations would have revealed our error.

When we consider the relatively high figures for the incidence of carcinoma in cases of chronic ulcerative colitis published by some authors, it is evident that the problem is a serious one. Such data might be used to justify excision of the colon in all long-standing cases of the disease, as a prophylactic procedure against the development of a malignant process. In our opinion this would involve much needless surgery, and possibly loss of life, and a permanent artificial stoma would be necessary. On the basis of the facts presented, it is difficult to accept without question the direct relation of pseudopolyposis and chronic ulcerative colitis to carcinoma. On the contrary, our own observations indicate that carcinoma, when it does develop in a case of pseudopolyposis with chronic ulcerative colitis, probably occurs as an entirely independent phenomenon, possibly on the basis of a preexisting adenoma. We have never noted the development of a true neoplastic adenomatous polyp from an inflammatory pseudopolyp. Further support of the lack of relation between carcinoma and pseudopolyposis is offered by control studies in cases of carcinoma without chronic ulcerative colitis.

SUMMARY

A series of 855 cases with chronic ulcerative colitis, including 134 with pseudopolyposis, is presented. Clinical and pathologic studies failed to reveal a single case of carcinoma. It is suggested that the latter may occur as an entirely independent phenomenon, possibly on the basis of a preexisting adenoma.

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SURVIVAL AFTER RECENT MYOCARDIAL INFARCTION

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AND

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RECENTLY we have analyzed the factors concerned with the immediate prognosis in recent myocardial infarction¹. In this report we wish to present the results of our analysis on the long term prognosis. Of the 572 cases previously reported, 507 were selected for this study. These patients were the ones seen in the hospital during the period from 1940 to 1945, inclusive. They represent 0.43 per cent of the total admissions for these years. The selection of these cases was based on the electrocardiographic findings, correlated with the clinical data and, when available, with the necropsy observations. Considerable reliance was placed on unmistakable signs of recent myocardial infarction in the electrocardiogram. The follow-up observations on these patients were made through private physicians, the hospital outpatient department or direct correspondence with the patients known to be alive. Seventeen of the 507 patients could not be followed. A number of the patients had died by the time of the follow-up study, which was made in January 1947. It was possible to obtain complete follow-up data, including electrocardiograms, on 100 of these patients. Our findings in the latter group will be the subject of another communication². Information as to the status of patients who could not

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1. Mintz, S. S., and Katz, L. N. Recent Myocardial Infarction. An Analysis of Five Hundred and Seventy-Two Cases, *Arch. Int. Med.* 80:205 (Aug.) 1947.

2. Mills, G. Y., Cisneros, F., and Katz, L. N. Observations on One Hundred Patients with Myocardial Infarction Who Survived Up to Six Years, *Arch. Int. Med.* to be published.

be contacted for personal interviews was obtained from their private physicians or from the records of the outpatient department. In the case of the patients who died in the interim, an effort was made to determine as closely as possible the data on and the circumstances concerned with their death. This information was obtained from the private physician's records, from members of the family or, in some instances, from the hospital record obtained on a subsequent terminal

TABLE 1—*Mortality and Survival Rate of 507 Patients with Recent Myocardial Infarction Occurring from 1940 to 1945, Followed for Various Periods Up to More Than Six Years**

1	2	3	4	5	6	7	8	9
Period, Months	Total in Group, No	Total Known Deaths, No	Death Rate, per Cent	Unable to Trace After Period Indi- cated, No	Followed Only for Months Indi- cated and Known to Be Alive, No	Total Followed and Con- dition Known, No	Known to Be Alive at End of Period	
							No	per Cent
First 2	488	135	27.6	81		488	353	72.3
2-6	272	22	8.1	7		407	250	61.4
6-12	243	23	9.5	11	24	400	220	55.0
12-24	185	15	8.1	11	40	365	170	46.6
24-36	119	13	10.9	7	32	314	106	33.7
36-48	67	3	4.5	2	14	275	64	23.3
48-60	48	6	12.5	3	17	259	42	16.2
60-72	22	0	0	1	17	239	22	9.2
More than 72	4	0	0	0	0	221	4	
Cumulative totals for deaths	488	217	81.2					

* We were unable to trace 19 patients, and do not know their span of life.

admission. Thus, we were able to obtain a complete follow-up study on 19 per cent of the patients, 3 per cent could not be traced, and some information was obtained on the remaining 78 per cent, of whom 59 per cent were known to be dead and 41 per cent were alive at the time of the follow-up study.

RESULTS

Mortality and Survival Rate—The first problem considered was the relation of survival and mortality rates at various periods after the occurrence of the infarct. These data are assembled in table 1. It will be seen that of the 488 patients followed, 217, or 44.6 per cent, had died. The mortality rate was greatest in the first two months, being

27.6 per cent. This is higher than the 8 per cent reported by Master and his associates,³ the 15 per cent reported by Drake⁴ or the 16.2 per cent reported by Connor and Holt,⁵ but is of the order reported by Howard.⁶ The rate after the first two months lessened progressively.⁷ It will be seen that the greatest mortality rate occurred in the first year and was less, and more or less steady, during the second to the fifth year. The cumulative mortality rate illustrated in figure 1 shows that by the end of the fifth and sixth years, 81 per cent of the patients would be dead, and only 19 per cent would survive a period of five to six years. Obviously, the totals in the group followed after the

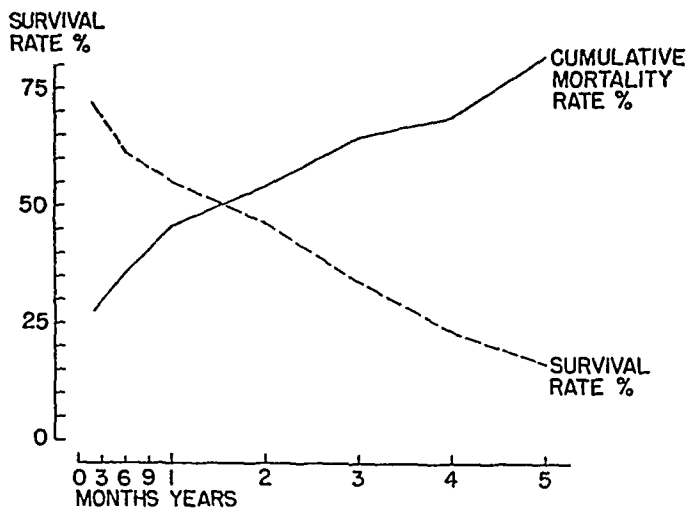


Fig 1—Cumulative mortality rate and survival rate at various periods after myocardial infarction (table 1)

3 Master, A. M., Jaffe, H. L., and Dack, S. Treatment and Immediate Prognosis of Coronary Artery Thrombosis (Two Hundred and Sixty-Seven Attacks), *Am Heart J* **12** 549, 1936

4 Drake, E. H. Long Survival Following Coronary Thrombosis, *Am Heart J* **20** 634, 1940

5 Connor, L. A., and Holt, E. The Subsequent Course and Prognosis in Coronary Thrombosis (An Analysis of Two Hundred and Eighty-Seven Cases), *Am Heart J* **5** 705, 1930

6 Howard, T. Coronary Occlusion, Based on the Study of One Hundred and Sixty-Five Cases, *M Times & Long Island M J* **62** 337, 1934

7 To obtain the mortality rate for the later intervals given in column 4, we first obtained the total in the group observed in the periods concerned (shown in column 2). This was done by subtracting from the total of the previous period (in column 2) the sum of the known dead in that period (in column 3) plus those unable to be traced after that period (in column 5) and those who were followed only for the period indicated (in column 6) because the follow-up was not extended beyond January 1947.

fifth year are too small to be considered quantitative in any sense. That this estimate of survival time is correct is shown by another calculation, given in columns 7, 8 and 9 of table 1. Here are presented the number and percentage of patients known to be alive at the end of each period. The percentage survival is also presented in figure 1. It was found that 72 per cent of the patients survived the first two months after infarction, by the end of the year the survival rate was 55 per cent, and by the end of the five years it was only 16 per cent. Our data on survival rate at the end of five years are lower than those reported by Connor and Holt⁵ and Levine and Rosenbaum⁸ on smaller series.

It appears from our observation that roughly one fourth of the patients having a recent myocardial infarction would be dead at the end of two months. About one half would be dead at the end of the year, about two thirds at the end of the third year and about four fifths at the end of five years. This surprisingly high mortality rate makes the long term prognosis of a recent myocardial infarction much more serious than has been anticipated generally.

Cause of Death After First Two Months Following Recent Myocardial Infarction—In this series, 82 patients are known to have died after the first two months following recent myocardial infarction. In 30 the cause of death was unknown. Of the remaining 52, 10 died of heart failure, 3 of pulmonary embolism, 34 of a new myocardial infarct and 5 of miscellaneous causes. In this series, there were apparently no deaths after the first two months from cerebral apoplexy or renal insufficiency. The diagnosis of the cause of death was based on the evaluation of the clinical findings, and when necropsy was obtained, on the autopsy findings. The data are summarized in table 2 and presented diagrammatically in figure 2. It is significant that 65 per cent of the patients who died after the first two months following recent myocardial infarction did so because of a new myocardial infarct. This is a higher rate than the 40 per cent reported by Levine and Rosenbaum⁸. Heart failure was a less common cause, accounting for 19 per cent, this is almost identical with the rate reported by Levine and Rosenbaum⁸. Pulmonary embolism was responsible for almost 6 per cent.

The fatal new myocardial infarct occurred most commonly in the first year after the infarction, but instances occurred in every year up to five years. More significant is the fact that all the pulmonary

8 Levine, S. A., and Rosenbaum, F. F. Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. Ultimate Prognosis, *Arch Int Med* 68:1215 (Dec) 1941.

emboli that were fatal occurred in the first year. On the other hand, the deaths due to heart failure were distributed more evenly over the five year period. One can conclude, therefore, that the hazard of pulmonary embolism is remote after the first year following infarction,

TABLE 2—*Causes of Death of the 82 Patients Who Succumbed After First Two Months Following Recent Myocardial Infarction**

Period of Survival, Months	Heart Failure	Pulmonary Emboli	New Myocardial Infarct	Miscellaneous	Unknown	Total
2-6	1	2	11	2	6	22
6-12	2	1	8	1	11	23
12-24	3	0	5	1	6	15
24-36	2	0	5	1	5	13
36-48	1	0	2	0	0	3
48-60	1	0	3	0	2	6
60-84	0	0	0	0	0	0
Totals	10	3	34	5	30	82
Per cent of total deaths	12.2	3.7	41.4	6.1	36.6	
Per cent of deaths of known cause	19.2	5.8	65.4	9.6		

* The diagnoses of cause of death are based principally on findings at necropsy, and when no postmortem examination was made, on clinical judgment. There were apparently no deaths due to cerebral apoplexy or renal insufficiency.

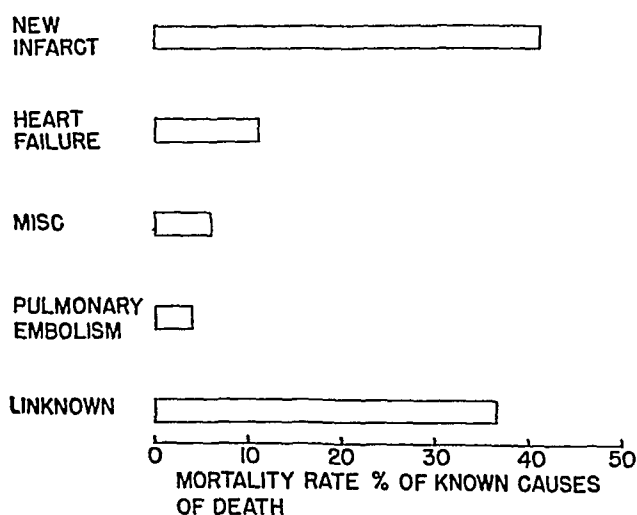


Fig 2—Frequency of known causes of death two months after recent myocardial infarction (table 2)

that heart failure will be the terminal event at any time during the first five years and that the most significant cause of death, recurrent myocardial infarction, may also occur at any time in the five year period, but most frequently in the first year after the original infarction.

Effect of Various Factors on Long Term Mortality Rate of Recent Myocardial Infarction—In table 3 and in figure 3 are summarized our

TABLE 3—*Effect of Various Factors on the Long Term Mortality Rate for Recent Myocardial Infarction, Based on an Analysis of 507 Cases Occurring Between 1940 and 1945*

Factors	Total Cases, No	Total Cases in Follow up Study, No	Total Deaths in First 2 Months		Total Deaths in Entire Period		Total Deaths After Second Month		Average Duration of Life of Those Known to Have Died, Months	Average Duration of Life of Those Who Died After 2 Mo, Months	Alive But Could Not Be Contacted, No
			No	Per Cent of Total No of Cases	No	Per Cent of Total No of Cases	No	Per Cent of Total No of Cases			
Known hypertension before and at admission	256	194	71	27.7	127	49.6	56	21.9	8.8	15.5	22
Known angina pectoris up to 1 mo prior to, or at admission	171	124	37	21.6	69	40.8	32	18.7	9.0	16.8	20
Clinical heart failure at admission	127	108	61	48.0	91	71.6	30	23.6	7.1	14.5	6
Known diabetes mellitus before or at admission	63	57	32	50.8	43	63.3	11	17.5	2.9	7.1	4
Electrocardiogram showing low voltage, ectopic rhythms, block and/or sinus tachycardia on admission	212	163	77	36.3	105	49.5	28	13.2	6.7	13.0	14
Electrocardiogram showing normal voltage, rhythms of sinus origin (exclusive of tachycardia) and no ectopic beats or block on admission	295	215	57	19.3	107	36.2	50	16.9	10.3	21.5	37
Patient asymptomatic on admission	88	55	19	21.5	25	23.4	6	6.9	12.4	44.3	14
Total group	507	488	135	26.6%	217	42.8%	82	16.2%	8.2 mo	17.8 mo	117

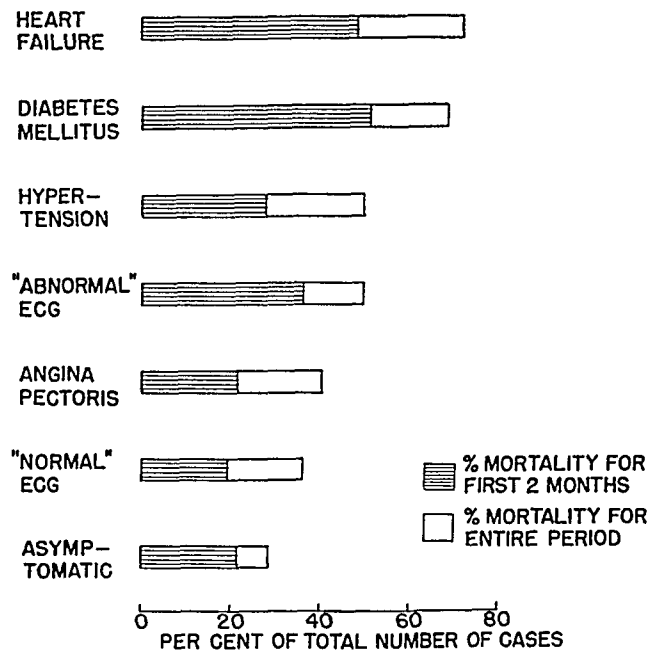


Fig 3—Effect of various factors on mortality rate (table 3)

experiences with several factors which might influence the long term mortality rate of recent myocardial infarction. We analyzed the effect of the following factors: (1) the presence of known hypertension (150 systolic and 90 diastolic, or over) before or at admission, (2) the presence of known angina pectoris at the time of admission and up to a month prior to admission, (3) the influence of clinical heart failure on admission, (4) the effect of known diabetes mellitus present before or on admission, (5) the influence of a cardiac status reflected by certain electrocardiographic abnormalities, such as low voltage, ectopic rhythms, heart block and/or sinus tachycardia present in the electrocardiogram on admission, (6) the influence of a cardiac status reflected by an electrocardiogram obtained on admission with normal voltage, rhythm of sinus origin (exclusive of tachycardia) and not showing block or ectopic beats, and (7) the significance of the lack of symptoms pointing to recent myocardial infarction on admission.

In order to make comparisons possible, the figures for the entire group of 507 patients are listed at the bottom of table 3. It was found that 26.6 per cent of all the patients died in the first two months and that 42.8 per cent died during the total period of observation, so that 16.2 per cent of the entire group died after the second month. The total duration of life of the known dead of the entire group averaged 8.2 months and the total duration of life of those who died after the second month was 17.8 months. These figures for duration of life are lower than those reported by others.⁸

Hypertension. By comparison with the entire group, it will be seen that hypertension had no effect on the mortality rate in the first two months,⁹ but had a slight deleterious influence on the later mortality (the rate being 49.6 per cent for the group with hypertension as against 42.8 per cent for the entire group, and the rate after the second month being 21.9 per cent as against 16.2 per cent for the entire group). Furthermore, in the group with hypertension the duration of life of those who died after two months was shortened slightly (14.5 months as compared with 17.8 months for the entire group). Our results indicate therefore that while hypertension has no effect on immediate mortality in the first two months—a finding in agreement with previous observations,⁹ it seems to decrease the long term survival slightly. This

9 (a) Mintz and Katz.¹ (b) Gross, H., and Engelberg, H. Essential Hypertension. A Comparison of the Hypertensive and Non-Hypertensive Phase Following Coronary Thrombosis, *Am J M Sc* 199:621, 1940.

last finding is in accord with some previous reports,¹⁰ but others¹¹ indicated no such effect

Angina Pectoris The presence of angina pectoris had no deleterious effect on the immediate mortality in the first two months (in agreement with our previous observations¹ or on the long term mortality rate, although the average duration of life of those who died after two months was slightly shortened

Heart Failure The presence of heart failure on admission not only sharply increased the mortality rate in the first two months, as has been noted previously¹² (the mortality rate being 48 per cent as compared with 26.8 per cent for the entire group), but also increased the over-all mortality rate (71.6 per cent as compared with 42.8 per cent) and the mortality rate after the second month (23.6 per cent compared with 16.2 per cent). Heart failure, furthermore, significantly shortened the duration of life of those who died after the second month (14.5 months as compared with 17.8 months). Thus, it is apparent that heart failure strikingly worsens the prognosis, both immediately and over the five year period. This has been reported previously¹³

Diabetes Mellitus Diabetes, as previously found,¹⁴ strikingly increased the mortality rate in the first two months (50.8 per cent as

10 (a) Master, A. M., Dack, S., and Jaffe, H. L. Coronary Thrombosis: Investigation of Heart Failure and Other Factors in Its Course and Prognosis, *Am Heart J* **13** 330, 1937. (b) Rosenbaum, F. F., and Levine, S. A. Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. I. Immediate Prognosis, *Arch Int Med* **68** 913 (Nov) 1941.

11 (a) Levine and Rosenbaum.⁸ (b) Vander Veer, J. B., and Brown, L. E. Diagnosis and Prognosis of Coronary Occlusion, *Electrocardiogram As Aid*, Pennsylvania M. J. **39** 303, 1936. (c) Bedford, D. E. Prognosis in Coronary Thrombosis, *Lancet* **1** 223, 1935. (d) Chambers, W. N. Blood Pressure Studies in One Hundred Cases of Coronary Occlusion with Myocardial Infarction, *Am J M Sc* **213** 40, 1947. (e) Bland, E. F., and White, P. D. Coronary Thrombosis (with Myocardial Infarction) Ten Years Later, *J A M A* **117** 1171 (Oct 4) 1941. (f) Gross and Engelberg.^{9b}

12 Mintz and Katz.¹ Rosenbaum and Levine.^{10b}

13 Levine and Rosenbaum.⁸ Rosenbaum and Levine.^{10b}

14 (a) Mintz and Katz.¹ (b) Gross and Engelberg.^{9b} (c) Root, H. F., Sharkey, T. P. Coronary Arteriosclerosis in Diabetes Mellitus, *New England J Med* **215** 605, 1936. (d) Root, H. F., Bland, E. F., Gordon, W. H., and White, P. D. Coronary Atherosclerosis in Diabetes Mellitus. A Post Mortem Study, *J A M A* **113** 27 (July 1) 1939. (e) Rabinowitch, I. M. Arteriosclerosis in Diabetes. Effects of High Carbohydrate-Low Calorie Diet, *Ann Int Med* **8** 1436, 1935. (f) Blotner, H. Coronary Disease in Diabetes Mellitus, *New England J Med* **203** 709, 1930. (g) Enklewitz, M. Diabetes and Coronary Thrombosis. Analysis of Cases Which Came to Necropsy, *Am Heart J* **9** 386 1934.

compared with 26.6 per cent) and also the over-all mortality rate (68.3 per cent as compared with 42.8 per cent). However, the long term mortality rate was not greatly altered, the mortality rate after the first two months being 17.5 per cent as against 16.2 per cent for the whole group. But the average duration of life for the patients who died after two months was greatly shortened (7.1 months as compared with 17.8 months). Apparently, the presence of diabetes, while not increasing the mortality rate after two months, led to earlier death among those that did die. It is also significant that diabetes sharply reduced the duration of life of the known dead over the entire period of study even more strikingly (2.9 months as compared with 8.2 months), suggesting that even in the patients who died in the first two months the ill effects occurred sooner than in the whole group. We may conclude therefore that, by and large, the ill effects of diabetes so far as death is concerned manifest themselves early in the period after infarction and that the later prognosis is no worse than for the group as a whole. Therefore, a diabetic patient who survives the first six or eight months after the infarction has no worse a prognosis than the nondiabetic patient.

Certain Electrocardiographic Abnormalities The influence of certain abnormalities in the electrocardiogram listed in the fifth line of table 3 was definitely to increase the mortality rate in the first two months (36.3 per cent as compared with 26.6 per cent). This is in accord with the observations previously reported by us¹ except that we had not previously analyzed the data for the factor of low voltage. The ill effects of auriculoventricular block,¹⁵ intraventricular block¹⁶ and low voltage¹⁷ were noted previously, but other authors^{10b} considered low voltage a favorable sign. In this group the mortality rate after the first two months was not significantly different than that for the whole group, so that the mortality rate for the entire period was influenced only by the greater mortality in the first two months. Apparently, however, the average duration of life was shortened both for all

15 (a) White, P. D., and Bland, E. F. A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis. A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, *Am Heart J* **7** 1, 1931. (b) Stone, C. T. Future of Patient with Coronary Occlusion, *New Orleans M & S J* **95** 305, 1943.

16 (a) White and Bland^{15a} (b) White, P. D. The Prognosis of Angina Pectoris and of Coronary Thrombosis, *J A M A* **87** 1525 (Nov 6) 1926. (c) Stone^{15b}

17 Barnes, A. R. Electrocardiogram in Myocardial Infarction. Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, *Arch Int Med* **55** 457 (March) 1935.

those who died during the period of study and for those who died after two months (6.7 months as compared with 8.2 months and 12 months as compared with 17.8 months). All electrocardiographic abnormalities have been considered to be of poor prognostic significance at one time or another,¹⁸ especially when more than one of them occurs simultaneously.¹⁹ Levine,²⁰ however, suggested that auricular fibrillation has no influence on prognosis. We may conclude, therefore, from our data that the presence of low voltage, ectopic rhythms, heart block and/or sinus tachycardia on admission has no effect on the mortality rate after the first two months, but definitely increases the mortality rates for the first two months. Thus, those patients in this group who survive the first six or eight months have as good a prognosis as the whole group.

Electrocardiograms Without Low Voltage or the Aforementioned Abnormalities Patients with electrocardiograms which on admission failed to show low voltage or the abnormal rhythms considered in the preceding paragraph showed a much better prognosis as regards the immediate mortality rate (19.3 per cent as compared with 26.6 per cent), but their mortality rate after the first two months was no better than that for the group as a whole (16.9 per cent as compared with 16.2 per cent). Conner and Holt,⁵ however, indicated that patients with normal rhythm and voltage had a better long term prognosis. The better over-all prognosis in terms of mortality rate is due, therefore, to the more optimistic outlook in the first two months. This also explains why the over-all duration of life for those who died in this group was

¹⁸ (a) Rosenbaum and Levine^{10b} (b) Master, A. M., Dack, S., and Jaffe, H. L. Disturbances of Rate and Rhythm in Acute Coronary Thrombosis, *Ann Int Med* **11** 735, 1937 (c) Partial and Complete Heart Block in Acute Coronary Occlusion, *Am J M Sc* **196** 513, 1938, (d) Age, Sex and Hypertension in Myocardial Infarction, Due to Coronary Occlusion, *Arch Int Med* **64** 767 (Oct) 1939 (e) Salcedo-Salgar, J., and White, P. D. Relationship of Heart Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris, and Coronary Thrombosis, *Am Heart J* **10** 1067, 1935 (f) Levine, S. A. Coronary Thrombosis Its Various Clinical Features, *Medicine* **8** 245, 1929 (g) Willius, F. A., and Killins, W. A. The Occurrence and Significance of the Electrocardiograms of Low Voltage, *Arch Int Med* **40** 332 (Sept) 1927 (h) Master, A. M., Dack, S., and Jaffe, H. L. Bundle Branch Block in Acute Coronary Artery Occlusion, *Am Heart J* **16** 283, 1938 (i) Woods, R. M., and Barnes, A. R. Factors Influencing Immediate Mortality After Coronary Occlusion, *ibid* **24** 4, 1942

¹⁹ Ken, W. J. The Present Status of Electrocardiography in the Diagnosis, Prognosis and Treatment of Heart Disease, *California & West Med* **23** 417, 1925

²⁰ Levine, S. A. Coronary Thrombosis Its Various Clinical Features, *Medicine Monographs*, Baltimore, Williams & Wilkins Company, 1929, vol 16

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1947 to July 1948

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(Continued from Page 720)

TABLE OF CONTENTS

9 Vagotomy	Congenital Atresia
Historical Aspects	Enteric Cyst
Anatomic Relations	Hernia
Physiologic and Other Effects	Regional Enteritis
Clinical Results of Vagotomy	Acute Jejunitis
Comment	Nonspecific Ulcers
Sympathectomy and Splanch-	Tuberculosis
nicectomy	Steatorrhea and Sprue
10 Duodenum	Absorption of Fat
Motility	Absorption and Transport of Iron
Congenital Defects	Intestinal Lipodystrophy
Diverticula	Endometriosis
Cysts	Intussusception
Arterioesenteric Occlusion	Intestinal Obstruction
Duodenitis	Viability of Strangulated Bowel
Removal of Foreign Bodies	Intestinal Intubation
Miscellaneous Disorders	Redundant Postoperative Segments
Benign and Malignant Tumors	Leakage from Enterostomy
11 Small Intestine	Vascular Disease
Motility	Scleroderma
Gas	Mesenteric Thrombosis
Roentgenologic Examination	Perforation, Traumatic Resection
Diverticula, Including Meckel's	and Foreign Bodies
Diverticulum	Benign and Malignant Tumors

VAGOTOMY

The tremendous interest in vagotomy is reflected in the more than seventy papers included in the present review

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, The School of Medicine

Historical Aspects—Small⁵⁰¹ DeCourcy⁵⁰² and Alvarez⁵⁰³ present highly informative summaries of the historical aspects of this operation. Interest in the procedure apparently dates back many years, although the completeness of the vagotomy performed has been questioned by various observers.

Anatomic Relations—Chamberlin and Winship,⁵⁰⁴ in a necropsy study of the vagus nerves, found that in 60 per cent of bodies they fell into a simple pattern, a single trunk representing the right or posterior nerve, in 16 per cent they formed a pattern in which single trunks were formed, but two or more secondary trunks were present above the esophageal hiatus, in 12 per cent they were of a complex pattern, with more than one primary trunk.

Walters and his associates⁵⁰⁵ and Bradley,⁵⁰⁶ on the basis of a similar investigation, conclude that in 92 per cent of cadavers distinct right and left gastric nerves were identified at the esophageal hiatus, in 8 per cent, the arrangement of one or both gastric nerves was abnormal and irregular, identification of such nerves in gastric vagotomy would necessitate the thoracic approach. Dragstedt and his associates⁵⁰⁷ also describe the course of the vagus nerves over the lower portion of the esophagus and present in detail their technic of transabdominal vagotomy. Doubilet and others⁵⁰⁸ conclude that vagal section can be complete either at the infra-aortic level or at the diaphragmatic hiatus. The reviewers venture to suggest that anatomic studies, valuable as they are, do not answer the question of the incidence of completeness in vagotomy, either supradiaphragmatic or infradiaphragmatic. Accurate physiologic studies are needed not only immediately after operation but years later.

501 Small, J. T. Symposium on Peptic Ulcer Denervation of the Stomach, Arch Surg **55** 189 (Aug) 1947.

502 DeCourcy, J. L. A Century and a Third of Vagotomy, Cincinnati J Med **29** 199, 1948.

503 Alvarez, W. C. Sixty Years of Vagotomy. A Review of Some Two Hundred Articles, Gastroenterology **10** 413, 1948.

504 Chamberlin, J. A., and Winship, T. Anatomic Variations of the Vagus Nerves. Their Significance in Vagus Neurectomy, Surgery **22** 1, 1947.

505 Walters, W., Neibling, H. A., Bradley, W. F., Small, J. T., and Wilson, J. W. Anatomic Distribution of the Vagus Nerves at Lower End of the Esophagus. Relation to Gastric Neurectomy for Ulcer, Arch Surg **55** 400 (Oct) 1947.

506 Bradley, W. F. Gastric Neurectomy (Vagotomy) in Treatment of Duodenal Ulcer. Anatomic Considerations, Minnesota Med **31** 256, 1948.

507 Dragstedt, L. R., Fournier, H. J., Woodward, E. R., Tovee, E. B., and Harper, P. V. Transabdominal Gastric Vagotomy, Surg, Gynec & Obst **85** 461, 1947.

508 Doubilet, H., Shafiroff, B. G. P., and Mulholland, J. H. The Anatomy of the Peri-Esophageal Vagi, Ann Surg **127** 128, 1948.

Physiologic and Other Effects—Clarke, Storer and Dragstedt⁵⁰⁹ found that the continuous nocturnal secretion of gastric juice in the empty stomach of patients with benign ulcer is, as a rule, greater in volume than that of patients without ulcer, it is greatly reduced after section of the vagus nerves. The secretory response to insulin hypoglycemia and to a meal is abolished by the section. The pronounced decrease in gastric motility observed in the two weeks after operation disappears within one to three months.

Dragstedt and others⁵¹⁰ state that complete division of the vagus nerves in cases of ulcer produces complete and permanent relief of the distress. The relief is not due to anesthesia of the stomach, for the introduction of a solution of hydrochloric acid into the stomach during the first three or four days after operation reproduces the pain with its previous intensity. Trauma to the vagus nerves does not produce pain. The sensation of hunger is not abolished by complete vagotomy, inflation of a balloon in the stomach produces a feeling of distention or actual pain.

Schoen and Griswold⁵¹¹ note that although basal secretion and gastric emptying were greatly decreased by vagotomy, histamine accelerated the rate of secretion and increased the concentration of pepsin and acid. The cephalic stimulus of sham feeding was noted before but not after operation, and peptic power actually decreased. Insulin-stimulated secretion was reduced. The basal secretory rate was decreased by approximately 36 per cent. Crandell and his associates⁵¹² report a diminished response to the alcohol test meal. There was no change in the electroencephalographic pattern for patients after vagotomy, nor was there any impairment of utilization or absorption of protein.

The postoperative insulin test (ten to fourteen days after operation) yielded a negative response for acid in 22 cases, a positive response in 3 and a doubtful reaction in 1.⁵¹³ Decreased motility was observed

509 Clarke, J. S., Storer, E. H., and Dragstedt, L. R. The Effects of Vagotomy on the Physiology of the Stomach in Patients with Peptic Ulcer, *J. Clin. Investigation* **26** 784, 1947.

510 Dragstedt, L. R., Woodward, R., Harper, P. V., and Storer, E. H. Mechanism of the Relief of Ulcer Distress by Gastric Vagotomy, *Gastroenterology* **10** 200, 1948.

511 Schoen, A. M., and Griswold, R. A. The Effect of Vagotomy on Human Gastric Function, *Ann. Surg.* **126** 655, 1947.

512 Crandell, W. B., Boehm, W. E., and Mulholland, J. H. Effects of Supra-Diaphragmatic Section of the Vagus Nerves in Man, *Arch. Surg.* **55** 343 (Sept) 1947.

513 Stein, I. F., Jr., and Meyer, K. A. Studies on Vagotomy in the Treatment of Peptic Ulcer, *Surg., Gynec. & Obst.* **86** 473, 1948.

in the majority Eight cases were restudied three to nine months after operation, with results similar to those obtained earlier, except in 1 case, in which ulcer symptoms recurred, positive secretory and motility responses to insulin were obtained

Brody and Quigley ⁵¹⁴ describe a method for the accurate registration of the intraluminal pressures within the upper portion of the gastrointestinal tract An almost complete loss of so-called phasic pressure waves after vagotomy was observed in 1 case

Monsangeon ⁵¹⁵ found that vagotomy did not abolish the sensation of hunger There was no tendency toward spasm at the cardiac or pyloric orifices Roentgenologic examination of the gallbladder, performed soon after operation in 2 cases, indicated that the gallbladder was evacuated within twenty to forty minutes, delayed evacuation of the dye was observed in 3 cases six to nine months after vagotomy

A group of 29 patients with transthoracic section and of 4 with transabdominal resection of the vagus nerves was studied roentgenographically ⁵¹⁶ In the early postoperative stages there was definite gastric dilatation and atonicity in most subjects Sluggish, ineffective and arrhythmic peristalsis, or absence of peristalsis, was associated with the dilatation and atonicity Emptying time, both initial and final, was greatly increased The changes occurred to a lesser degree in patients with previous gastroenterostomy and in those with partial gastrectomy There was a return toward the normal within a period of six months to a year Complete return to normal in all respects was not observed in any case, 1 was followed for fourteen months The ulcers, especially the stomal and jejunal ulcers, healed promptly The postoperative size of the small bowel was not remarkable, the motility was slow, apparently because of the delay in gastric emptying Dysphagia developed temporarily in 1 case

Feldman and Morrison ⁵¹⁷ suggest the possible development of a roentgenologic insulin test for the completeness of vagotomy Mandl and Mannchen ⁵¹⁸ describe a new test for complete vagotomy Sym-

514 Brody, D A, and Quigley, J P Intralumen Pressures of the Stomach and Duodenum in Health and Disease, *Gastroenterology* **9** 570, 1947

515 Monsangeon, A Vagotomy for Ulcers, *Semaine d hop*, Paris **24** 303, 1948

516 Ritvo, M, and Shauffer, I A Roentgenographic Studies of the Gastrointestinal Tract Following Section of the Vagus Nerves for Peptic Ulcer, *New England J Med* **238** 496, 1948

517 Feldman, M, and Morrison, S The Effect of Insulin on Motility of the Stomach Following Bilateral Vagotomy, *Am J Digest Dis* **15** 175, 1948

518 Mandl, F, and Mannchen Ein neuer Test fur die effektiv durchgefuhrt Vagotomie bei Ulkuskkrankheit, *Wien med Wchnschr* **98** 97, 1948

pathetic block on the right side at the levels of the seventh and eighth thoracic segments results in an increase in both the total acidity and the free acidity because the elimination of sympathetic stimuli results in a preponderance of vagal activity, accompanied with increased acidity and motility. The hypothesis was tested in 21 cases, the acid values increased after sympathetic block with incomplete vagotomy but remained unchanged after complete vagotomy. The procedure is therefore recommended as a test for complete vagotomy.

Transient hypertension developed after vagotomy in 2 cases.⁵¹⁹ Szasz⁵²⁰ concludes that vagotomy provides healing of ulcer without gratification of the patient's emotional needs and that medical management should be continued for psychologic reasons, rather than for physiologic or medical reasons. The reviewers find this concept interesting but not convincing.

Clinical Results of Vagotomy—Moses,⁵²¹ in a critical review of one hundred and forty-four papers, concludes that, although vagotomy results in "semipermanent cures," the mechanism is unknown and its permanence not yet measured. He states the belief that vagotomy should be the procedure of choice in cases of marginal ulcer and in those of duodenal ulcer penetrating into the pancreas or involving the area of the common bile duct. Ruffin and White⁵²² report that vagotomy affords gratifying and dramatic relief of symptoms in the majority of cases of "intractable" peptic ulcer. Recurrences have been reported in a small percentage of cases, in a few, patients have not been relieved of their symptoms. Bockus⁵²³ adopts a conservative view. Johnson and Machella⁵²⁴ and Wilbur, Cheney and Carleton⁵²⁵ conclude that the operation is not indicated in gastric ulcer, that it may be indicated in duodenal ulcer, and that its principal value appears to be in ulcer recurrent after gastric resection and gastroenterostomy. Smith⁵²⁶ condemns vagus section or palliative procedures for prepyloric

519 Marcussen, J. M. Temporary Hypertension Reaction After Vagotomy, *Nord med* **38** 1222, 1948.

520 Szasz, T. S. Psychiatric Aspects of Vagotomy. A Preliminary Report, *Ann Int Med* **28** 279, 1948.

521 Moses, W. R. Critique on Vagotomy, *New England J Med* **237** 603, 1947.

522 Ruffin, J. M., and White, P. The Present Status of Vagotomy in the Treatment of Peptic Ulcer, *Gastroenterology* **10** 607, 1948.

523 Bockus, H. L. Recent Advances in Treatment in Field of Gastroenterology, *J A M A* **136** 293 (Jan 31) 1948.

524 Johnson, J., and Machella, T. E. Vagotomy for the Treatment of Peptic Ulcer, *Clin North America* **27** 1406, 1947.

525 Wilbur, D. L., Cheney, G. C., and Carleton, M. Clinical Conference of Vagotomy, *M Clin North America* **32** 301, 1948.

526 Smith, G. K. Benign and Malignant Prepyloric Lesions of the Stomach, *California Med* **68** 86, 1948.

gastric lesions, in view of the difficulty in differentiation between benign and malignant lesions Grimson and others⁵²⁷ state the conclusion that transthoracic vagotomy alone should not be used as standard treatment for duodenal or gastric ulcer, but that vagotomy may be of value when combined with gastroenterostomy or when employed for stomal ulcer

Dragstedt⁵²⁸ reports excellent results in a series of 212 cases It is emphasized that the possibility of cancer makes the surgical problem of benign gastric ulcer different from that of duodenal or jejunal ulcer⁵²⁹ In 3 cases of coexistent gastric and duodenal ulcer and in 3 cases of ulcer high on the lesser curvature of the stomach, prompt healing was obtained after vagotomy In the remaining 2 cases, the differential diagnosis between ulcer and cancer could not be made even at laparotomy, the ulcer failed to heal after vagotomy The patient in 1 of these cases died of cerebral hemorrhage, there was evidence of active ulcer, but an autopsy was not obtained The other patient, still under observation at the time of the report, had an ulcer three months later, secretory studies indicated that the vagotomy had been complete

Moore⁵³⁰ obtained satisfactory results in 90 per cent of cases Sanders⁵³¹ confirms the conspicuous reduction in secretion, tonus, hunger contractions and relief of pain Thorlakson⁵³² indicates a favorable impression with the results of 63 vagotomies Orr and Johnson⁵³³ describe good or excellent results in all of 34 cases of duodenal ulcer in

527 Grimson, K S , Baylin, G J , Taylor, H M , Hesser, F H , and Rundles, R W Symposium on Peptic Ulcer Clinical Evaluation of Complications Observed After Transthoracic Vagotomy, *Arch Surg* **55** 175 (Aug) 1947

528 Dragstedt, L R , Harper, P V , Jr , Tovee, E B , and Woodward, E R Section of the Vagus Nerves to the Stomach in the Treatment of Peptic Ulcer, *Ann Surg* **126** 687, 1947

529 Harper, P V , Jr , and Dragstedt, L R Section of the Vagus Nerve to the Stomach in the Treatment of Benign Gastric Ulcer, *Arch Surg* **55** 141 (Aug) 1947

530 Moore, F D Vagus Resection for Ulcer An Interim Evaluation, *Ann Surg* **126** 664, 1947

531 Sanders, R L An Evaluation of the Methods of Surgical Treatment of Duodenal Ulcer, *South M J* **40** 567, 1947, Bilateral Segmental Vagal Resection in the Treatment of Peptic Ulcer, *ibid* **13** 493, 1947

532 Thorlakson, P H T The Surgical Management of Chronic Duodenal Ulcer with Special Reference to the Role of Vagotomy, *Canad M A J* **58** 561, 1948

533 Orr, I M , and Johnson, H D Vagal Resection in the Treatment of Duodenal Ulcer, *Lancet* **2** 84, 1947

which vagotomy was regarded as complete. The outcome in 16 cases in which incomplete vagotomy was performed was recorded as fair to excellent in 12 and poor in 4. Favorable conclusions are reported by numerous authors.⁵³⁴

Vagotomy with pyloroplasty or gastroenterostomy is safer and more effective than gastric resection alone, according to Crile⁵³⁵. Gardner⁵³⁶ reports good results from partial gastrectomy and vagotomy; the resection is relatively small and is performed to obviate retention after vagotomy. Franksson,⁵³⁷ under the heading "Selective Abdominal Vagotomy," describes an attempt to cut branches to the upper part of the stomach, leaving the rest of the fibers intact. Postoperative insulin tests, apparently done ten days after operation, showed absence or decrease of free hydrochloric acid. The ulcer decreased in size or healed in each instance. In spite of these results, the reviewers cannot accept the rationale of the procedure because of the general observation that a single intact fiber is sufficient to activate the entire mechanism of gastric secretion. Johns and Grose⁵³⁸ report an unsatisfactory outcome in 7 cases after vagotomy alone; in 3 recurrent pain occurred (in 2 the vagotomy was incomplete, as shown by insulin test), and in 3, gastric retention. Patients subjected to a combination of vagotomy and enterostomy or resection experienced uniformly good results.

534 Seabrook, D. B. Surgical Treatment of Peptic Ulcer, *Rocky Mountain M J* **45** 26, 1948. Wulff, H. B. Vagotomy for Peptic Ulcer. Theoretic Background and Clinical Results, *Acta chir Scandinav* **96** 265, 1947. Lowe, E. S. Vagotomy in the Treatment of Peptic Ulcers, *U S Nav M Bull* **47** 785, 1947. Cole, W. H., Walter, L., and Reynolds, J. Vagotomy in the Treatment of Peptic Ulcer, *South Surgeon* **13** 870, 1947. Thompson, V. C., and James, A. H. Vagotomy for Peptic Ulcer, *Lancet* **2** 44, 1947. Dumont, R. Notes preliminaires sur l'operation de Dragstedt (vagotomie transthoracique), *Acta gastroenterol belg* **10** 498, 1947. Collins, E. N., and Stevenson, C. W. Bilateral Vagotomy in the Treatment of Peptic Ulcer, *Gastroenterology* **10** 205, 1948. Harkins, H. N. The Present Status of Vagotomy in Surgical Treatment of Peptic Ulcer, *Northwest Med* **46** 945, 1947. Boerema, I. Direct Results of Vagotomy in Presence of Gastric Complaints Following Operation on Account of Ulcer, *Nederl tijdschr v geneesk* **92** 1755, 1948.

535 Crile, G. Transabdominal Vagotomy Versus Gastric Resection in the Treatment of Duodenal Ulcer, *Cleveland Clin Quart* **14** 264, 1947.

536 Gardner, C. Simultaneous Vagotomy and Partial Gastrectomy for Intractable Peptic Ulcer, *Canad M A J* **58** 137, 1948.

537 Franksson, C. Selective Abdominal Vagotomy, *Acta chir Scandinav* **96** 409, 1948.

538 Johns, T. N. P., and Grose, W. F. Symposium on Vagotomy for Peptic Ulcer. II. Early Surgical Results in Forty-Three Cases, *Bull Johns Hopkins Hosp* **81** 92, 1947.

Paulson and Gladsden⁵³⁹ noted no significant gastroscopic change after vagotomy except a decrease in peristaltic activity and a more patulous-appearing antium. In those cases in which subtotal gastric resection had also been performed, the edema, nodule-like hypertrophy and friability were similar to those observed in the cases without vagotomy. Attempts to determine the influence of vagotomy on pancreatic activity by means of serum amylase levels showed no conclusive change. Important questions are raised concerning the validity and importance of the insulin test, including the difficulty of interpretation after gastroenterostomy, the problem of whether all vagal fibers can be interrupted anatomically and the possibility that all fibers need not be cut to produce satisfactory clinical results. It is concluded that relief of symptoms, decreased volume of gastric secretion, alterations in gastric tone and motility and results of the test for gastric acidity cannot be utilized as criteria for the completeness of vagotomy. Moore⁵⁴⁰ reports that 87 per cent of 74 patients were satisfied with the results of vagotomy two to thirty months after operation. Five patients had recurrent ulcer, the side effects experienced by 5 others were of sufficient magnitude to detract from the value of the operation.

Thorek⁵⁴¹ performed vagotomy in 25 cases, deaths occurred in 3, none being attributable to the operation. One patient died of a perforated jejunal ulcer seven weeks after subtotal gastric resection and vagotomy. Cameron⁵⁴² reports a case in which a gastric ulcer developed, with perforation and death, sixteen days after vagotomy for chronic duodenal ulcer. In 15 cases described by Warren,⁵⁴³ mild symptoms of retention were noted in 2, a recurrent duodenal ulcer with two additional gastric ulcers necessitating gastric resection developed in 1 case. Four failures were encountered by Harkins and Hooker⁵⁴⁴ in 36 cases in which vagotomy was performed.

539 Paulson, M., and Gladsden, E. S. Medical Aspects of Vagotomy for Peptic Ulcer Including Observation on the Clinical Value of the Insulin Test and on Postoperative Criteria for the Completeness of Bilateral Gastric Vagus Section, *Bull Johns Hopkins Hosp* **81** 107, 1947.

540 Moore, F. D. Resection of the Vagus Nerves for Ulcer. An Interim Evaluation, *Arch Surg* **55** 164 (Aug.) 1947.

541 Thorek, P. Vagus Nerve Section (Vagotomy) in the Treatment of Peptic Ulcers. Review of Literature and Report of Personal Cases, *J. A. M. A.* **135** 1141 (Dec. 27) 1947.

542 Cameron, D. A. Vagotomy for Peptic Ulcer, *Am J M Sc* **214** 202, 1947.

543 Warren, R. Experience with Vagotomy for Peptic Ulcer, *Surgery* **22** 246, 1947.

544 Harkins, H. N., and Hooker, D. H. Vagotomy for Peptic Ulcer, *Surgery* **22** 239, 1947.

Meyer and his associates⁵⁴⁵ noted immediate relief from pain due to ulcer after vagotomy in 35 cases in which there had been no previous response to medical or surgical treatment. Thirty-one patients were leading an unrestricted life and were well satisfied with the results at the time of the report. One patient died of uremia and nephrosis after a blood transfusion. Recurrent symptoms with roentgenologic evidence of active ulcer developed in 4 cases, and symptoms of cardiospasm, subsiding spontaneously, were noted in 3.

Hansen⁵⁴⁶ performed vagotomy alone or with gastroenterostomy, gastric resection or miscellaneous procedures in 52 cases. Pleural effusion occurred in all of 10 cases in which treatment was by transthoracic vagotomy. One patient died of a perforated esophagus with generalized peritonitis, aspiration pneumonia and mediastinitis on the fifth postoperative day. Abdominal distention developed in 12 cases and diarrhea, in 9. The volume of the nocturnal gastric secretion among male patients decreased from 568 to 325 cc and among female patients from 446 to 240 cc. Postoperative roentgenologic studies indicated a persistent ulcer in 6 cases. Derom⁵⁴⁸ noted gastric atony and dilatation in 3 of 6 cases. In 1, a gastric ulcer recurred temporarily ten months after the operation. Hallenbeck and Priestley⁵⁴⁹ describe 2 unsatisfactory cases, pain and hemorrhage continued in 1, and gastric retention necessitated gastroenterostomy in the second. Other authors⁵⁵⁰ express varied opinions.

545 Meyer, K. A., Rosi, P. A., and Stein, I. F., Jr. Studies on Vagotomy in Treatment of Peptic Ulcer. II. Clinical Evaluation, *Surg, Gynec & Obst* **86** 524, 1948.

546 Hansen, A. M. Vagotomy, *Ann West Med & Surg* **2** 249, 1948.

547 Footnote deleted on proof.

548 Derom, E. L'atonie et la dilatation gastriques apres vaguectomie de Dragstedt dans l'ulcus gastro-duodenal, *Acta gastroenterol belg* **11** 58, 1948.

549 Hallenbeck, D. A., and Priestley, J. T. Transthoracic Vagotomy. Notes on Unsatisfactory Results in Two Cases, *Proc Staff Meet, Mayo Clin* **22** 332, 1947.

550 Illingworth, C. F. W., and Kay, A. W. Vagotomy in the Treatment of Peptic Ulcer, *Edinburgh M J* **54** 540, 1947. Woodruff, R., and Hunter, R. T. Indications for Vagus Nerve Resection in the Treatment of Peptic Ulcer, *Rocky Mountain M J* **44** 523, 1947. Castleton, K. B. Vagotomy in the Treatment of Peptic Ulcer, *ibid* **44** 698, 1947. Fox, S. F. Resection of Vagus Nerves in Treatment of Peptic Ulcer, *J Maine M A* **39** 149, 1948. Plaschkes, S. J. Vagus-resektion als Ulcusoperation, *Gastroenterologia* **73** 240, 1948. Orban, F., and Dalem, J. Le place actuelle de la vagotomie dans le traitement de l'ulcere gastro-duodenale, *Rev med Liege* **3** 129, 1948. Blackford, S. D., and McCourland, A. Results of Vagotomy, *Virginia M Monthly* **75** 265, 1948.

Walters and his associates ⁵⁵¹ describe their experience in a series of articles, stating the conclusion that the greatest value of vagotomy is in the treatment of recurrent ulcer after partial gastrectomy. The operation is considered to have no place in the management of gastric ulcer ^{551a}. The relief of pain after vagotomy is attributed to the subsidence of "gastrospasm" and to the reduction of gastric acidity. The reviewers insist that "gastrospasm" is not a proved factor in pain due to ulcer, whereas the role of acidity is proved. In another article, ^{551d} 3 cases of ulcer symptoms are reported in which results of the insulin test were negative after vagotomy, in 2 of these, an ulcer was demonstrated roentgenologically. In another case in which the results of the insulin test were negative, an unhealed jejunal ulcer was found at operation several months after vagotomy. The authors state ^{551f} that they consider the results of vagotomy to be inconstant and unpredictable, they regard the procedure as in the experimental stage. Among 80 patients so treated there were 5 deaths, 4 of which were attributed to the operation. Seven patients were troubled by the persistence or recurrence of peptic ulcer or by gastric atony with pronounced retention. In a later report, ^{551g} the same authors review their results up to May 1, 1947, in 118 cases. Vagotomy alone was performed in 48, gastrojejunostomy having been performed previously in 14, ulcer pain persisted in 2. Vagotomy and an additional gastric operation (partial resection, pyloroplasty, gastroenterostomy or excision of gastric ulcer) were carried out in 70 patients, ulcer distress continued in 5. There were 6 deaths, 2 of which were not assigned to the operation. Recurrence of the ulcer or failure of the lesion to heal within three weeks was reported in 13 cases of the entire group. In 15 per cent of the series, symptoms of disturbed motility were noted nine months or more after vagotomy.

Comment—Clearly, there is no unanimity of opinion concerning the present status of vagotomy. Many investigators report excellent results and advocate the procedure for treatment of all types of benign peptic

551 (a) Walters, W., Neibling, H. A., Bradley, W. F., Small, J. T., and Wilson, J. W. Favorable and Unfavorable Results of Gastric Neurectomy (Vagotomy) for Peptic Ulcer. An Anatomic, Physiologic and Clinical Study, *S. Clin. North America* **27**: 885, 1947. (b) Walters, W. Vagotomy for Peptic Ulcer, *Proc. Staff Meet., Mayo Clin.* **22**: 281, 1947. (c) Walters, W., Neibling, H. A., Bradley, W. F., and Small, J. T. A Study of the Results Both Favorable and Unfavorable of Section of the Vagus Nerves in the Treatment of Peptic Ulcer, *Ann. Surg.* **126**: 679, 1947. (d) Walters, W., Neibling, H. A., Bradley, W. F., Small, J. T., and Wilson, J. W. Vagotomy in Peptic Ulcer, *Minnesota Med.* **30**: 965, 1947. (e) Gastric Neurectomy for Gastric and Duodenal Ulceration, *Ann. Surg.* **126**: 1, 1947. (f) Gastric Neurectomy. Anatomic and Physiologic Studies with Favorable and Unfavorable Results in Treatment of Peptic Ulcer, *Arch. Surg.* **55**: 151 (Aug.) 1947. (g) Results of Vagus Nerve Resections in Treatment of Peptic Ulcer, *J. A. M. A.* **136**: 742 (March 13) 1948.

ulcer Others, while recording good or satisfactory results in the majority of cases, direct attention to the untoward physiologic effects encountered in occasional cases Data on persistence and recurrence of symptoms at variable intervals after vagotomy now are being recorded, accurate correlation of these results with the completeness or incompleteness of the operation is not possible, although the impression is gained that in the majority of instances, at least, the vagus section has been incomplete There is almost unanimous agreement in favor of vagotomy for treatment of ulcer recurrent after gastric resection or gastroenterostomy A majority of writers seem to recommend combining the operation with gastroenterostomy for duodenal ulcer with cicatricial stenosis, although the possibility of recurrent ulcer is not excluded Others advocate vagotomy for duodenal ulcer not responding to medical management or manifesting "vagal hyperactivity" A majority of clinicians are opposed to its use in gastric ulcer, chiefly because of the difficulties in differentiation of benign and malignant ulcer It may also be noted, in this connection, that the principal benefit of vagotomy apparently lies in the elimination of the cephalic phase of hypersecretion, the output of acid in patients with gastric ulcer is not excessive and, indeed, is quite similar to that observed in normal persons Vagotomy, in the opinion of the reviewers, is not a substitute for careful medical management, it should not be employed indiscriminately Experience to date suggests, however, that vagotomy and gastroenterostomy are preferable to gastric resection in cases of chronic recurrent duodenal ulcer and high grade cicatricial stenosis All observers agree as to the necessity of a more prolonged period of observation before the ultimate value of the operation can be assessed accurately, it is highly important, therefore, to study carefully each patient, diagnostically, clinically and physiologically

Sympathectomy and Splanchnicectomy — Torre and Villareal⁵⁵² describe a case of essential hypertension, in which treatment by a Smithwick sympathectomy was followed with an urge to defecate The symptom was attributed to increased vagal effect, resulting from the section of the sympathetic nerves Roentgenologic examination disclosed increased gastric peristalsis, six hours later the large bowel was filled with barium sulfate Splanchnicectomy for hypertension was performed in the case of a man who had experienced "heartburn" for fifteen years, "hypermotility and spasm" of the duodenal bulb had been diagnosed roentgenologically⁵⁵³ After the operation, the heartburn disappeared,

552 Torre, J M, and Villareal, R Radiological Changes in the Gastrointestinal Tract of a Patient Following the Smithwick Operation, *Gastroenterology* **10** 543, 1948

553 Siris, J H Amelioration of Peptic Ulcer Symptoms Following Splanchnicectomy, *New York State J Med* **48** 640, 1948

the hypertension returned four and one-half years later. The reviewers question the interpretation of the author, who apparently relates the disappearance of the heartburn directly to the splanchicectomy.

DUODENUM

Motility—Mathur and his associates⁵⁵⁴ found that hunger contractions in the duodenum of fasting dogs are temporarily inhibited by cutaneous stimuli and by the sight and smell of food. Contractions, suggesting the occurrence of reverse peristalsis from jejunum to duodenum, were recorded immediately prior to vomiting. Borisov⁵⁵⁵ reports that denervation of the renal pedicle in dogs is followed by atony of the stomach and duodenum.

Congenital Defects—Nelson⁵⁵⁶ describes a congenital diaphragm of the duodenum, treated by resection.

Forshall⁵⁵⁷ reports the cases of 4 newborn infants with duodenal obstruction, located above the ampulla of Vater in 2 and below the ampulla in 1, in the fourth case, there were a cyst of the jejunum and nonrotation and volvulus of the entire small bowel. Two of the 4 patients were operated on successfully. Stewart⁵⁵⁸ states the belief that early vomiting of bile-stained material without abdominal distention is the essential diagnostic point. Benson and Penberthy⁵⁵⁹ treated 2 patients satisfactorily by means of posterior gastroenterostomy and duodenojejunoscopy, respectively. Patton⁵⁶⁰ successfully treated, by longitudinal myotomy, 2 patients with congenital hypertrophic stenosis of the first portion of the duodenum. Congenital and so-called secondary and functional enlargements of the duodenum are discussed by Hillemand and Dugue⁵⁶¹.

554 Mathur, P. D., Grindlay, J. H., and Mann, F. C. Observations on Duodenal Motility in Dogs with Special Reference to Activity During Vomiting, *Gastroenterology* **10** 866, 1948.

555 Borisov, M. V. Influence of Denervation of the Renal Pedicle on the Motor Functions of the Duodenum, *Khirurgiya*, 1947, no. 1, p. 22.

556 Nelson, W. I. Congenital Diaphragm of Duodenum. Case Report with Preoperative X-Ray Studies, *Minnesota Med* **30** 245, 1947.

557 Forshall, I. Duodenal Obstruction in the Newborn, *Brit J Surg* **35** 58, 1947.

558 Stewart, J. S. Congenital Extrinsic Duodenal Obstruction in the Newborn, *South Surgeon* **14** 15, 1948.

559 Benson, C. D., and Penberthy, G. C. Congenital Duodenal Obstruction, *Arch Surg* **56** 58 (Jan) 1948.

560 Patton, E. F. Congenital Hypertrophic Stenosis of the Duodenum, *J. Pediat* **32** 301, 1948.

561 Hillemand, P., and Dugue, M. A propos du megaduodenum, *Arch. d. mal. de l'app. digestif* **36** 129, 1947.

Diverticula—The various aspects of diverticula of the duodenum and jejunum are reviewed in detail⁵⁶² Slater and Parsons⁵⁶³ and Whitmore⁵⁶⁴ conclude that diverticula of the duodenum seldom give rise to symptoms

Cysts—Three cases of enterogenous cyst of the duodenum are described⁵⁶⁵

Arteriomesenteric Occlusion—Metz⁵⁶⁶ and Graver⁵⁶⁷ both discuss the syndrome of arteriomesenteric occlusion of the duodenum with duodenal regurgitation into the stomach, characterized by recurring attacks of nausea and vomiting, with loss of weight The positive diagnosis is based on observation of the dilated duodenum to the right of the spine, with delay of barium sulfate passing over the spine and with hyperperistalsis and regurgitation of the barium into the stomach The reviewers continue to be highly skeptical The syndrome, if it exists, must be extremely rare

Duodenitis—Diaz⁵⁶⁸ gives a bizarre picture of duodenitis

Removal of Foreign Bodies—Equen and others⁵⁶⁹ illustrate the removal of metallic foreign bodies from the duodenum by means of a magnet of aluminum, nickel, cobalt and iron, introduced under fluoroscopic guidance Mackby⁵⁷⁰ reports surgical removal of such a body

Miscellaneous Disorders—Two interesting cases are reported, 1 of perforation of the gallbladder into the duodenum, with duodenal obstruction by a gallstone, and 1 of probable congenital megaduodenum⁵⁷¹ Subcutaneous retroperitoneal rupture of the duodenum after

562 Mahorner, H, and Kirsner, W Diverticula of the Duodenum and Jejunum, Surg, Gynec & Obst **85** 607, 1947 D'Alotto, V Duodenal Diverticula, Prensa med argent **34** 1696, 1947

563 Slater, F M, and Parsons, W H The Surgical Aspects of Diverticula of the Duodenum, South Surgeon **14** 240, 1948

564 Whitmore, W H Duodenal Diverticula with Ulceration, Am J Roentgenol **59** 343, 1948

565 Lorber, S H, and Machella, T E Enteric Cyst of the Duodenum, Gastroenterology **10** 892, 1948 Peple, W L Enterogenous Cysts of the Duodenum, Ann Surg **127** 912, 1948

566 Metz, A R Duodenal Regurgitation, Arch Surg **55** 239 (Sept) 1947

567 Graver, F W Duodenal Ileus (Wilkie's Syndrome) Arterio-Mesenteric Ileus, Bull Vancouver M A **24** 116, 1948

568 Diaz, M J Observations on Duodenitis, Gac méd españ **21** 233, 1947

569 Equen, M, Gilliam, R, and Lineback, M Nail in Duodenum Removed by Magnet, J A M A **135** 432 (Oct 18) 1947 Equen, M Foreign Bodies in the Duodenum, South M J **41** 187, 1948

570 Mackby, M J Foreign Body in Second Portion of Duodenum Perforating Pelvis of Right Kidney, J Mt Sinai Hosp **14** 929, 1948

571 Hertz, J Obstruction of the Duodenum with Special Reference to Gallstone Perforations, Acta chir Scandinav **96** 233, 1947

trauma is reported⁵⁷² "Pure" duodenal secretion of swine is reported to contain a factor with anti-pernicious-anemia properties⁵⁷³

Benign and Malignant Tumors—An adenoma of the first portion of the duodenum apparently produced the clinical features of a duodenal ulcer⁵⁷⁴ Fibroadenomatous benign polyps, arising in Brunner's glands, are described by Wilensky⁵⁷⁵ and by Tedesco and others⁵⁷⁶ Coppla and Chimanto⁵⁷⁷ report a polyp, Allison and Babcock,⁵⁷⁸ a lipoma, the patient having had a history of intermittent tarry stools for two years

The roentgenologic features of neoplasms of the duodenal and paraduodenal region are described by Kline and Culver⁵⁷⁹ Emphasis is placed on the presence of a small filling defect and on destruction or distortion of the mucosal pattern Carcinoma of the duodenum is discussed by Jessen,⁵⁸⁰ Lapeyre and others,⁵⁸¹ and Mendl and Tanner⁵⁸² Poer⁵⁸³ reports a lymphosarcoma of the duodenum, simulating perforated ulcer

SMALL INTESTINE

Motility—Helm and his associates⁵⁸⁴ noted a definite decrease in intestinal motility after the spontaneous onset of sleep, although the degree and character of the change was not constant Cycloheptenyl-

572 Lauritzen, G K Subcutaneous Retroperitoneal Duodenal Rupture, *Acta chir Scandinav* **96** 97, 1947

573 Landboe-Christensen, E, and Bohn, C L S On the Curative Effect of Pure Duodenal Secretion from Swine in Cases of Pernicious Anemia, *Acta med Scandinav* (supp 205) **130** 311, 1948

574 Swynghedauw and Salembier Tumeur benigne du duodenum, *Presse med* **56** 61, 1948

575 Wilensky, A O Tumors Arising in Brunner's Glands, *Am J Digest Dis* **15** 206, 1948

576 Tedesco, B, Leibovici, R, and Dausse, C Tumeur benigne du bulbe duodenal, *Arch d mal de l'app digestif* **37** 337, 1948

577 Coppola, J A, and Chimanto, A Polipo del duodeno, *Arch argent de enferm d ap digest y de la nutricion* **22** 256, 1947

578 Allison, T D, and Babcock, J R Lipoma of the Duodenum Causing Melena, *Ann Surg* **127** 754, 1948

579 Kline, J R, and Culver, G J Roentgen Findings in Primary Duodenal and Paraduodenal Malignant Lesions, *Am J Roentgenol* **58** 425, 1947

580 Jessen, K E Duodenal Cancer, *Nord med* **35** 1651, 1947

581 Lapeyre, N G, Ginestie, Groos, and Camp Cancer of the First Portion of the Duodenum, *Montpellier med* **31-32** 5, 1947

582 Mendl, K, and Tanner, C H Carcinoma of Duodenum, *Brit J Radiol* **21** 309, 1948

583 Poer, D H Lymphosarcoma of the Gastrointestinal Tract, *Surgery* **23** 354, 1948

584 Helm, J D, Kramer, P, McDonald, R M, and Ingelfinger, F J Changes in Motility of the Human Small Intestine During Sleep, *Gastroenterology* **10** 135, 1948

ethyl barbituric acid (medomin®) produced relaxation of excised segments of intestine and uterus of cats and dogs, the intact intestine responded with a decrease in tonus and a lessening of rhythmic contractions⁵⁴⁵

Hypermotility of the small intestine was noted in approximately 90 per cent of anesthetized dogs after rapid intravenous injections of acid and enzymatic hydrolysates, and of monosodium glutamate⁵⁸⁶ Solutions of amino acids with added glycine, essential for growth in rats, produced hypermotility in fewer instances (58 per cent) than did either acid and enzymatic hydrolysates or monosodium glutamate Normal, trained dogs did not vomit after the rapid injection of growth-essential amino acids plus glycine, but emesis was common after the administration of acid hydrolysates, enzymatic hydrolysates and monosodium glutamate The hyperglycemia which was present after rapid intravenous injections of hydrolysates or of solutions of growth-essential amino acids plus glycine largely disappeared after circulatory exclusion of the liver or after hepatectomy

Administration of tetraethylammonium produced no change in 4 patients with cardiospasm, or in persons with a normal esophagus⁵⁸⁷ Intravenous injection of the drug resulted in a prompt diminution of gastric muscular tone and in generalized dilatation of the stomach, similar to that observed after vagotomy Intravenous or intramuscular injections of the drug caused profound inhibition of the propulsive movements of the small bowel The mucosal markings appeared to be fixed in one position over a period of minutes or hours, depending on the size of the dose The drug produced no appreciable change in the haustral pattern of the large bowel, though it did allow the colon to become greatly distended without producing a desire to defecate Parenterally administered, the drug appeared to block the transmission of impulses through the autonomic ganglions, both sympathetic and parasympathetic Tetraethylammonium caused an immediate cessation, or a considerable decrease, in motility of the upper small bowel⁵⁸⁸ The

585 Halbeisen, W A , Gruber, C M , Jr , and Gruber, C M Effect of Cycloheptenylethyl Barbituric Acid, "Medomin," on Intestinal and Uterine Smooth Muscle, *Proc Soc Exper Biol & Med* **68**:343, 1948

586 Sokalchuk, A , Ellis, D , Westei, M R , Weston, K , Greisheimer, E M , and Oppenheimer, M J Comparative Effects of Protein Hydrolysates and Amino Acid Mixtures on Intestinal Motility and Blood Sugar Levels After Rapid Intravenous Injection, *Gastroenterology* **10** 831, 1948

587 Holt, J F , Lyons, R H , Neligh, R B , Moe, G K , and Hodges, F J X-Ray Signs of Altered Alimentary Function Following Autonomic Blockade with Tetraethylammonium, *Radiology* **49**:603, 1947

588 Chapman, W P , Stanbury, J B , and Jones, C M The Effect of Tetraethylammonium on the Small Bowel of Man, *J Clin Investigation* **27** 34, 1948

effect was apparently identical to that of atropine given under the same control conditions. Thresholds for intestinal pain, elicited by balloon distention, were unchanged after administration of tetraethylammonium. The value of the drug as a relaxing agent is limited by its brief duration of action.

Five antihistaminic compounds were effective, in nontoxic doses, in preventing histamine-induced spasm of the ileum in dogs⁵⁸⁹. The exposure, *in vitro*, of strips of feline small intestine to soft roentgen radiation, varying in quantity from 1,000 to 10,000 r, apparently did not influence significantly their kymographically recorded motility⁵⁹⁰.

Gas—Morris, Ivy and Maddock⁵⁹¹ noted comparatively large intragastric and intraesophageal negative pressures during inspiration. By voluntarily relaxing the superior esophageal sphincter, air could be aspirated. It is apparent that under certain conditions, considerable amounts of air may enter the upper portion of the gastrointestinal tract without the act of swallowing.

The incidence of abdominal pain due to the expansion of intestinal gas at high altitude was studied in healthy young subjects making simulated flights to 38,000 feet (11,400 meters) in a low pressure chamber⁵⁹². Discomfort was noted in 28.2 per cent of attempts, but distress was serious in only 5.5 per cent. Large volumes of gas were sometimes tolerated without pain. The ingestion of melons and carbonated drinks immediately before flight was consistently associated with the occurrence of pain. Diets high in carbohydrate increased the incidence and severity of pain, whereas high protein diets decreased the incidence and severity of pain. These effects were not due to an alteration in the volume of intestinal gas. In further experiments, it was found that gas immediately above or below the ileocecal valve was most likely to produce pain.

The formation of gas in the closed intestines of cats was measured after the introduction of chemotherapeutic and antibiotic agents⁵⁹³. The smallest amounts were found after the administration of penicillin and, to a lesser extent, of sulfonamide drugs, the effect of streptomycin was variable.

589 Craver, B. N., Cameron, A., and Yonkman, F. F. Comparative Effectiveness of Five Antihistaminics Versus Histamine Induced Spasm in Canine Thiry-Vella Loops, *J. Pharmacol. & Exper. Therap.* **93** 168, 1948.

590 Craver, B. N. The Effect of Roentgen Rays on the *in Vitro* Motility of Feline Intestine, *Am. J. Roentgenol.* **58** 357, 1947.

591 Morris, C. R., Ivy, A. C., and Maddock, W. G. Mechanism of Acute Abdominal Distention, *Arch. Surg.* **55** 101 (Aug.) 1947.

592 Blair, H. A., Dern, R. J., and Smith, V. G. Intestinal Gas in Simulated Flight to High Altitude, *J. Aviation Med.* **18** 352, 1947.

593 Schweinburg, F., Frank, E., Segal, A., and Fine, J. Gaseous Distention in the Obstructed Small Intestine of Cats, *Proc. Soc. Exper. Biol. & Med.* **67** 45, 1947.

Roentgenologic Examination—Hodges and his associates^{594a} advise against the overemphasis of the significance of minor alterations in the small bowel. In only a small percentage of cases of disorders of the small bowel can positive roentgenologic signs be found. Disease of the autonomic nerves, occurring as an isolated disorder or as one aspect of a more extensive neuropathy, may produce grave disturbances^{594b}

Diverticula, Including Meckel's Diverticulum—In a discussion of diverticulosis of the gastrointestinal tract, Nash and Palmer⁵⁹⁵ point out that diverticula of the first portion of the duodenum are rare, whereas pseudodiverticula secondary to ulcer spasm and scarring are common. Diverticula of the second and third portions of the duodenum are common, usually asymptomatic and rarely subject to complications but must be differentiated from neoplastic ulceration. Jejunal diverticula are rare, and usually asymptomatic. The incidence of Meckel's diverticulum is 1.5 to 3 per cent in the total population, it is twice as frequent in male as in female patients. Symptoms, when present, are usually those of obstruction or inflammation. In children, peptic ulceration with intestinal hemorrhage is the most frequent complication.

Maguire⁵⁹⁶ reaffirms the importance of considering the presence of Meckel's diverticulum in the cases of extremely young or old patients, in which there are obscure abdominal disorders and atypical findings, the complications of acute inflammation, hemorrhage, intussusception and obstruction are discussed. Instructive reviews and case reports are presented by other writers⁵⁹⁷. Multiple jejunal diverticula and their complications are discussed⁵⁹⁸.

594 (a) Hodges, F. J., Rundles, R. W., and Havelin, J. Roentgenologic Study of the Small Intestine. I. Neoplastic and Inflammatory Diseases, *Radiology* **49**:587, 1947, (b) II. Dysfunction Associated with Neurologic Disease, *ibid* **49**:659, 1947.

595 Nash, E. C., and Palmer, W. L. The Clinical Significance of Diverticulosis, Including Diverticulitis, of the Gastrointestinal Tract, *Ann Int Med* **27**:41, 1947.

596 Maguire, C. H. Meckel's Diverticulum as an Acute Surgical Emergency, *Arch Surg* **56**:65 (Jan) 1948.

597 Messenger, H. M., and Collins, E. N. Peptic Ulcer in Meckel's Diverticulum, *Cleveland Clin Quart* **14**:139, 1947. Murray, A. G. A Case of Massive Hemorrhage from Peptic Ulceration in a Meckel's Diverticulum, *M. J. Australia* **34**:145, 1947. Olaussen, T. Lesions in the Small Intestine Causing Melena, *Nord med* **37**:161, 1948. Taylor, S. Symptoms Due to Meckel's Diverticulum, *Lancet* **2**:786, 1947. Manning, V. R., Jr., and McLaughlin, E. F. Persistent Omphalomesenteric (Vitelline) Artery Causing Intestinal Obstruction and Gangrene of Meckel's Diverticulum, *Ann Surg* **126**:358, 1947. MacFarlane, D. A. Foreign Body Perforations in Meckel's Diverticulum, *Brit J Surg* **35**:421, 1948. Moses, W. R. Meckel's Diverticulum, *New England J Med* **237**:118, 1947. Wigers, F. Meckels divertikkel, *Nord med* **36**:2394, 1947.

598 Williams, C., and Boshier, L. H. Jr. Jejunal Diverticulosis Complicated by the Development of Jejuno-Colic and Jejuno-Jejunal Fistulas, *Ann Surg* **127**:918, 1948. Wilkerson, J. H., and Coffman, R. Multiple Diverticula of the Jejunum, *Am J Surg* **75**:733, 1948.

Congenital Atresia—Brynjulfson⁵⁹⁹ reviews atresia of the small and large intestine and reports 2 cases, both fatal, in which the condition was localized to the duodenum. He also reports a fatal case of multiple occurrence, and an instance of atresia of the small intestine with recovery after anastomosis. Potts⁶⁰⁰ and O'Neill and others⁶⁰¹ present further instructive case reports.

Enteric Cyst—A cyst arising from the antimesenteric border of the intestine, 3 feet (91 cm) from the ileocecal junction, is described⁶⁰²

Hernia—A paraduodenal hernia was diagnosed preoperatively in the case of a patient with recurrent attacks of cramping abdominal pain and vomiting⁶⁰³. On roentgenologic examination, the intestine had the appearance of being enclosed in a round, saclike structure on the right side of the abdomen. At operation, approximately two thirds of the small intestine was found to be in a retroperitoneal hernia arising at the duodenojejunal junction.

Regional Enteritis—Warren and Sommers⁶⁰⁴ in a study of 120 cases, observed obstruction of lymphatics and formation of granulomas in the intestinal wall and the lymph nodes. In the advanced or chronic state, submucosal edema, irregular hemorrhages in the mucosa and submucosa and mucosal ulceration were noted. The terminal pathologic picture included fibrosis, abscesses and fistulas.

Rachet and Busson⁶⁰⁵ are impressed with the role of "sensitivity."

Rossmiller and Messenger⁶⁰⁶ reviewed the findings in 55 cases of regional enteritis; follow-up studies were made in 40. Cramping abdominal pain, weight loss and diarrhea were the outstanding symptoms. The most common objective findings were a palpable mass, usually located in the right lower quadrant of the abdomen, fever, a

599 Brynjulfson, B. C. Intestinal Atresia, *Nord med* **36** 2401, 1947

600 Potts, W. J. Congenital Atresia of Intestine and Colon, *Surg, Gynec, & Obst* **85** 14, 1947

601 O'Neill, J. F., Anderson, K., Bradshaw, H. H., Lawson, R. B., and Hightower, F. Congenital Atresia of the Small Intestine in the Newborn. Report of Two Cases, with Review of Successfully Treated Intrinsic Obstructions of Small Bowel, *Am J Dis Child* **75** 214 (Feb.) 1948

602 Tedesco, V. E., and Connell, J. H. Enteric Cyst, *Am J Surg* **74** 226, 1947

603 Reeves, R. J., Moran, F. T., and Jones, P. A. Right Paraduodenal Hernia with Roentgen Diagnosis and Postoperative Recovery, *Am J Roentgenol* **59** 338, 1948

604 Warren, S., and Sommers, S. C. Cicatrizing Enteritis (Regional Ileitis) as a Pathologic Entity, *Am J Path* **24** 475, 1948

605 Rachet, J., and Busson, A. Enterite et enterocolite folliculaire et segmentaire, *Acta gastroenterol belg* **11** 192, 1948

606 Rossmiller, H. R., and Messenger, H. M. Regional Enteritis. Diagnosis and Treatment, a Study of Fifty-Five Cases Over a Nine-Year Period, *M Clin North America* **32** 419, 1948

draining sinus of the abdominal wall and/or a fistula in ano. Short circuiting operations without transection of the bowel distal to the anastomosis and proximal to the diseased segment proved unsatisfactory, favorable results were obtained after resection. Appelmans and his associates⁶⁰⁷ conclude, after a review of 40 cases, that the most satisfactory treatment is wide resection in a single stage procedure.

A fatal instance of enterocolitis, involving both the small and large intestine, is reported in a child of 1 month⁶⁰⁸. Histologic demonstration of chronic inflammation, fibrosis and hypertrophy of the bowel suggested that the process had begun in utero.

The occurrence of regional enteritis in 2 members of the same family, father and son, is described by Kirsner and others⁶⁰⁹. Other interesting cases are reported⁶¹⁰. In the case of a patient with extensive chronic enteritis involving the jejunum, ileum and colon, miliary and submiliary tubercles with caseation were observed in the liver, spleen, lungs, adrenals and mesenteric lymph nodes at autopsy⁶¹¹. Acid-fast organisms resembling tubercle bacilli were found in some of these lesions, but a primary focus was not demonstrated. The propriety of classifying this condition as "regional enteritis" seems debatable.

Osteomalacia was present in all of 16 cases in male patients with regional enteritis⁶¹², the process was mild in 36 per cent, moderate in 55 per cent and pronounced in 9 per cent. A similar finding was noted in 71 per cent of 7 cases in female patients. Regional enteritis involving segments of the entire small bowel, diagnosed at laparotomy, apparently subsided under conservative management, including the administration of penicillin and streptomycin⁶¹³. The subject is reviewed by Merke⁶¹⁴ and by Hillemand⁶¹⁵.

607 Appelmans, R., Van Goidsenhaven, P., and Fannes. De ileitis van Crohn, Konink Vlaamse Acad v geneesk Verhandel **9** 425, 1947.

608 Koop, C. E., Perlingiero, J. G., and Weiss, W. Cicatrizing Enterocolitis in a New Born Infant, Am J M Sc **214** 27, 1947.

609 Kirsner, J. B., Owens, F. M., and Humphreys, E. M. Regional Enteritis in Father and Son, Gastroenterology **10** 883, 1948.

610 Forney, J. M., Eskridge, M., and Shaver, J. S. Regional Enteritis, South M J **40** 732, 1947. Raffensperger, E. C. Recurrence of Regional Ileitis Associated with Pregnancy, Gastroenterology **10** 1010, 1948. Janus, W. L. Regional Jejunitis, Radiology **50** 532, 1948.

611 Gould, S. F. A Case of Regional Enteritis, Am J Clin Path **17** 955, 1947.

612 Bonorino Udaondo, C., and Castex, M. R. Ileítis regional y trofismo óseo, Prensa méd argent **34** 1523, 1947.

613 Corbett, R. A. Regional Ileitis Treated with Streptomycin, Rocky Mountain M J **44** 821, 1947.

614 Merke, F. Weitere Beobachtungen über die Ileitis terminalis, Schweiz med Wchnschr **77** 751, 1947.

615 Hillemand, P. L'ileite terminale, Presse med **56** 424-A (June 16, supp) 1948.

Hirschberg⁶¹⁶ notes a similarity between the symptoms of chronic enteritis and those of the postgastroenterostomy syndrome

Acute Jejunitis—Brekke⁶¹⁷ describes 9 cases of phlegmonous lesions of the small intestine, including 5 involving the terminal ileum. One case, given in detail, is that of a girl of 10, at operation, involvement was observed from the ligament of Treitz to the middle of the small intestine. No resection was attempted. Biopsy of a node revealed nonspecific inflammation, and culture yielded hemolytic streptococci. The use of penicillin apparently led to recovery. In 14 cases in which the diagnosis was acute jejunitis,⁶¹⁸ the roentgen signs were reduced movement of one or both sides of the diaphragm, distended loops of small bowel with fluid levels, persistently irregular pattern of the jejunal mucosa and delayed emptying of the affected loops. Twenty-one cases of acute jejunitis and 16 of acute regional enteritis are described.⁶¹⁹ The author states the belief that acute jejunitis occurs more frequently than is recognized. Jejunitis is classified as acute phlegmonous jejunitis, with a high mortality, and as acute simple jejunitis, with a low mortality. Pyogenic bacteria are apparently of etiologic importance.

Nonspecific Ulcers—Evert and others⁶²⁰ state that nonspecific ulcers of the jejunum and ileum are characteristically solitary, although small groups are sometimes found. The etiology is unknown, there is little direct evidence to support the theories that the lesion is caused by infection, irritation from gastric secretions, trauma or vascular abnormalities. The symptoms are, for the most part, secondary to the complications of perforation, bleeding or obstruction. The mortality rate is high. The lesion has been recognized during life only after complication has led to surgical intervention. An additional case is described by Dumont.⁶²¹

Tuberculosis—Schaffner⁶²² reports a series of 109 consecutive cases of pulmonary tuberculosis in which the patients were operated on for acute or subacute abdominal conditions, 101 cases suggested the diag-

616 Hirschberg, F. Enteritis chronica-jejunitis and ileitis, *Nord med* **36** 2499, 1947

617 Brekke, A. Jejuno-ileitis phlegmonosa, *Nord med* **34** 827, 1947

618 Husebye, O. W. On Roentgenological Diagnosis of "Jejunitis Acuta Phlegmonosa," *Acta radiol* **29** 71, 1948

619 Brynjulfson, B. C. Jejunitis acuta-ileitis regionalis acuta, *Acta chir Scandinav* **96** 361, 1948

620 Evert, J. A., Black, B. M., and Dockerty, M. B. Primary Nonspecific Ulcers of the Small Intestine, *Surgery* **23** 185, 1948

621 Dumont, R. Hemorrhagie massive par ulcere simple du grêle, *Acta gastroenterol belg* **10** 112, 1947

622 Schaffner, V. D. Intestinal Tuberculosis, *Canad M A J* **57** 561, 1947

nosis of acute appendicitis and 8, that of obstructive lesions. Of the 101 patients with symptoms of appendicitis, 20 (19.8 per cent) were found to have tuberculosis of the appendix or of the ileocecal region.

The incidence of intestinal tuberculosis discovered at necropsy in cases of active pulmonary tuberculosis was 28 per cent.⁶²³ The incidence of intestinal perforation was 10.4 per cent and of obstruction, 12.5 per cent. A case of hyperplastic tuberculosis of the colon is described in a woman of 26, with a history of pleurisy and tuberculous lymphadenitis.⁶²⁴ At operation, the lesion was thought to represent cancer, histologic examination disclosed the correct diagnosis.

Sweany⁶²⁵ reports subjective improvement due to streptomycin in 2 proven cases and 9 suspected cases of tuberculous enteritis. Markoff⁶²⁶ presents a preliminary report of 5 cases, however, the follow-up period was only six months.

Intestinal tuberculosis is comprehensively reviewed in twenty additional articles.⁶²⁷

623 Kornblum, S. A., Tale, C., and Aronson, W. Surgical Complications of Intestinal Tuberculosis as Seen at Necropsy, *Am J Surg* **75** 498, 1948.

624 Brodin, H. Case of Multiple Hyperplastic Tuberculosis of the Colon, *Acta radiol* **28** 227, 1947.

625 Sweany, H. C. Streptomycin in Tuberculous Enteritis, *Am Rev Tuberc* **56** 415, 1947.

626 Markoff, N. Die Streptomycinbehandlung der Darmtuberkulose, *Schweiz med Wchnschr* **78** 329, 1948.

627 Brohee, G., and Everaets, P. Radiologie et tuberculose iléo-cécale, *Acta gastroenterol belg* **10** 143, 1947. Warmoes, F., and Gyselen, A. La tuberculose jejuno-iléo-cécale. Point de vue clinique, *ibid* **10** 163, 1947. Courtois, R. La tuberculose jejuno-iléo-cécale. Point de vue social, *ibid* **10** 185, 1947. Tilmont, L. La tuberculose jejuno-iléo-cécale. Point de vue radiologique, *ibid* **10** 193, 1947. Van der Hoeden, R. La tuberculose jejuno-iléo-cécale. Point de vue biologique, *ibid* **10** 205, 1947. Firket, J., and Scaville, A. La tuberculose jejuno-iléo-cécale. Point de vue biologique, B. Anatomopathologie et bactériologie, *ibid* **10** 219, 1947. Goffin, R. La tuberculose jejuno-iléo-cécale. Thérapeutiques spéciales et chirurgie, *ibid* **10** 233, 1947. Maisin, J. La tuberculose jejuno-iléo-cécale. Thérapeutiques spéciales, B. radiothérapie, *ibid* **10** 249, 1947. Miché, J. La tuberculose jejuno-iléo-cécale. Thérapeutiques spéciales, C. physiothérapie, *ibid* **10** 257, 1947. Warmoes, F., DeWinter, L., and Gyselen, A. La tuberculose jejuno-iléo-cécale, Conclusions générales, *ibid* **10** 269, 1947. Warmoes, F. La tuberculose jejuno-iléo-cécale. Expériences personnelles du traitement de la tuberculose intestinale secondaire par les rayons ultra-violet, *ibid* **10** 302, 1947. Wilkinson, M. C. Intestinal tuberculosis, *ibid* **10** 313, 1947. Baumel, J. Quelques réflexions à propos de la tuberculose hypertrophique du cecum diagnostiquée et opérée comme cancer cécal, *ibid* **10** 315, 1947. Haak, A. Quelques mots sur la tuberculose ileo-cecale, *ibid* **10** 321, 1947. Rachet, J., Busson, A., and Arnous, J. Intérêt du peristaltisme provoqué dans le diagnostic radiologique de la tuberculose ileo-cecale, *ibid* **10** 324, 1947. Stephani, J. Radiologie et clinique

Steatorrhea and Sprue—Adlersberg and Schem⁶²⁸ describe 36 cases of "primary" sprue and 4 of steatorrhea secondary to other diseases. Four hundred cases of tropical sprue are reviewed by Elder⁶²⁹. The highest seasonal incidence in India, Assam and Burma is during May, June and July. Sprue may develop after only a short stay in the tropics. Fully established sprue may be present in the absence of steatorrhea. Treatment consisted in frequent small feedings of a diet low in fat, supplemented with nicotinic acid, riboflavin and liver.

Black and his associates⁶³⁰ carried out fat balance studies on 28 patients with early tropical sprue, determining percentage of fat absorbed by the expression
$$\frac{\text{dietary fat} - \text{fecal fat}}{\text{dietary fat}} \times 100$$
 In untreated sprue, fat absorption ranged from 51 per cent to 85 per cent, the normal being 90 per cent. Administration of nicotinic acid and riboflavin did not bring about improvement. After treatment with liver, improvement in fat absorption was not appreciable for some weeks. When yeast extract was given by mouth in large doses, some improvement occurred within twelve days. In a study of 30 early cases in Karachi, India, Howell⁶³¹ noted a high ratio of split fat to unsplit fat in most instances. During recovery the total amount of fecal fat often returned rapidly to normal limits, but the ratio lagged behind by one or two months.

In a series of 45 cases of idiopathic steatorrhea studied by Cooke and others⁶³² 33 patients had a red cell count above 2,500,000 per cubic millimeter and hemoglobin values exceeding 50 per cent. Ten had leukopenia. Of 17 sternal punctures, 4 were indistinguishable

de la tuberculose intestinale, *ibid* **10** 327, 1947. Bernard, A. Sûr un cas de tuberculose de l'intestin grêle, *ibid* **10** 330, 1947. Bernard, A. Tuberculose annehelle et intestinale, *ibid* **10** 334, 1947. Delannay, E. Evolution et ordre d'apparition des lésions tuberculeuses ileales et ileo-cecales, *ibid* **10** 339, 1947. Vaccarezza, R. F., Gofin-Moreno, I., Fernandez-Luna, D., Stapler, N. B., Capurro, F. G., and Nunez, C. G. Etiologia, anatomia patologica, diagnostico clinico, y radiologico y tratamiento de la tuberculosis intestinal, *Rev Asoc med argent* **62** 175, 1948.

628 Adlersberg, D., and Schem, J. Clinical and Pathologic Studies in Sprue, *J A M A* **134** 1459 (Aug 23) 1947.

629 Elder, H. H. A. Clinical Features, Diagnosis, and Treatment of Sprue, *J Trop Med* **50** 212, 1947.

630 Black, D. A. K., Bound, J. P., and Fourman, L. P. R. Fat Absorption in Tropical Sprue, *Quart J Med* **16** 99, 1947.

631 Howell, C. A. H. An Early Sign in Sprue, *Lancet* **2** 55, 1947.

632 Cooke, W. T., Frazer, A. C., Peeney, A. L. P., Sammons, H. G., and Thompson, M. D. Anomalies of Intestinal Absorption of Fat. II. The Hematology of Idiopathic Steatorrhea, *Quart J Med* **17** 9, 1948.

from those in pernicious anemia. Slight bilirubinemia was present in 8 patients. Free hydrochloric acid was present in the gastric content of 31 of 42 patients. Response to treatment with liver varied. The authors conclude that the macrocytic anemia of steatorrhea cannot be explained by the unitarian theory generally accepted in macrocytic anemias. In a study by Innes⁶³³ of the peripheral blood of 63 patients with the sprue syndrome, the characteristic picture in the adult was macrocytosis, with or without anemia. Macrocytosis tended to persist in spite of liver therapy. Hypochromic microcytic anemia was noted in celiac disease. In 9 of 18 cases in adults, the bone marrow was megaloblastic, the marrow was normoblastic in the 2 cases of celiac disease reported.

Observations on 6 patients with sprue during seven remissions following therapy with pteroylglutamic acid are summarized⁶³⁴. Each was characterized by relief of glossitis, with regeneration of lingual papillae, cessation of diarrhea, gain in weight and hematologic improvement. In 5 instances, a return toward a normal glucose tolerance was demonstrated. Improved absorption of vitamins and increased prothrombin concentration were noted. Two patients relapsed when administration of pteroylglutamic acid was withdrawn. Five milligrams of folic acid (pteroylglutamic acid) adequately maintained a patient with sprue⁶³⁵.

Parasites were found in the feces of 56 per cent of 25 patients with tropical sprue⁶³⁶. *Trichuris trichiura* and *Necator americanus* were the most common. The patients improved after the administration of folic acid, without antiparasitic therapy.

Contrary results are reported by Weir and Comfort⁶³⁷. Administration of folic acid, usually 50 mg daily by the intramuscular route, did not cause improvement in the sense of well-being or in gain in weight or strength in 5 cases. The frequency or severity of the exacerbations did not change, the anemia and macrocytosis persisted.

Osteomalacia secondary to steatorrhea in a woman of 61 progressed despite treatment with a low fat diet, supplemented with viosterol

633 Innes, E. M. The Blood and Bone Marrow in the Sprue Syndrome, *Edinburgh M. J.* **55** 282, 1948.

634 Darby, W. J., Jones, E., Warden, H. F., and Kasei, M. M. Influence of Pteroylglutamic Acid on Gastrointestinal Defects in Sprue, *J. Nutrition* **34** 645, 1947.

635 Vedder, E. B. A Case of Sprue Maintained on Folic Acid, *Am. J. Trop. Med.* **27** 723, 1947.

636 Milanes, F., Spies, T. D., Hernandez Beguerie, R., and Garcia Lopez, G. Some Observations on the Effect of Synthetic Folic Acid on the Alimentary Tract of Patients with Tropical Sprue, *Rev. Gastroenterol.* **15** 33, 1948.

637 Weir, J. F., and Comfort, M. W. Folic Acid Therapy in Nontropical Sprue. Results of Treatment in Seven Cases, *J. Lab. & Clin. Med.* **32** 1231, 1947.

(irradiated ergosterol) and calcium⁶³⁸ The parenteral administration of viosterol resulted in greater retention of calcium and in a rise in the blood calcium level

Glass⁶³⁹ concludes that the "small intestinal deficiency pattern" may be caused by many factors other than a deficiency of vitamin B complex Instances of prepyloric, pyloric and postpyloric lesions are described, in which disordered motor function of the small intestine was observed without specific disease of the small intestine

Absorption of Fat—Folic acid was shown to be of no value in improving the absorption of fat and nitrogen in dogs deprived of external pancreatic secretion⁶⁴⁰ Resection of the mesenteric lymph nodes in 10 dogs did not alter fecal fat and nitrogen excretion⁶⁴¹ In each dog, there was rapid reestablishment of anatomic and functional continuity of the mesenteric lymphatics Partial regeneration of the nodes occurred in 6 animals Alimentary lipemia curves were normal six to twelve days after operation in 3 of 4 dogs examined

Absorption and Transport of Iron—Gillman and Ivy,⁶⁴² in studies on guinea pigs, found that ferrous iron is converted into ferric iron immediately on contact with the saliva, it is conducted through the intestinal canal and is absorbed by the epithelium in ferric form The mononuclear phagocytic reticuloendothelial cells and the lymphatics are prominent in transporting iron from the intestine to the associated mesenteric lymph node The histologic changes occur in at least three phases In the first, the iron may be distinguished in the lumen of the bowel, nongranular, prussian blue-positive material can be seen clearly in the base of the epithelium This form of iron occurs during the first one to one and a half hours after feeding iron The second phase commences between three and six hours after feeding, there is an increase in the number of fine iron-containing granules in the luminal pole of the epithelial cells and in the amount of prussian blue-positive material immediately below the cuticular border The third phase,

638 Fourman, L P R, and Spray, G H Absorption of Vitamin D in Steatorrhea, Brit M J 1 142, 1948

639 Glass, W H Non-Vitaminic Factors Involved in the Production of the "Small Intestinal Deficiency Pattern," Gastroenterology 10 660, 1948

640 Douglas, G F, Jr, and Pratt, T D Fat and Nitrogen Absorption After Folic Acid Administration in Dogs Deprived of External Pancreatic Secretion, Proc Soc Exper Biol & Med 68 171, 1948

641 Clarke, B G, Ivy, A C, and Goodman, D Effect of Resection of Mesenteric Lymph Nodes on Intestinal Fat Absorption in the Dog, Am J Physiol 153 264, 1948

642 Gillman, T, and Ivy, A C Histological Study of the Participation of the Intestinal Epithelium, the Reticulo Endothelial System and the Lymphatics in Iron Absorption and Transport, Gastroenterology 9 162, 1947

initiated eight to twenty-four hours after feeding, continues for at least twenty-four to forty-eight hours. During this phase, iron cannot be detected in the cuticular border or in the lumen of the bowel. However, it can be seen in the epithelial cells, in both the granular and the nongranular (or diffuse) form, in the luminal half of the cells. Eight hours after feeding, there is an increased amount of iron in the phagocytes in the villi, these are practically confined to the tips of the villi, capping the lacteals and occasionally invading the epithelium.

Intestinal Lipodystrophy—Three cases of presumptive intestinal lipodystrophy (Whipple's disease), in which the patients were operated on because of an indefinite abdominal mass and in which the condition was diagnosed on the basis of the appearance of the mesentery at operation, are reported ⁶⁴³

Endometriosis—In two excellent papers, McGuff and his associates ⁶⁴⁴ review 16 cases of endometriosis causing intestinal obstruction and 48 similar cases described in the literature. The patients were largely between the ages of 30 and 50. The majority were sterile. Sigmoidoscopic examination revealed the lesion in 9 of 12 cases, roentgenograms of the colon revealed the process in 9 of 11 cases. The most important points in diagnosis are: acquired dysmenorrhea, menstrual irregularity, sterility, rectal or pelvic pain, absence of loss of weight, the presence of associated uterine fibroids or ovarian cysts and a long history of symptoms referable to the intestine and suggestive of progressive intestinal obstruction, with frequent exacerbations at menstruation. Severe constipation, pain low in the abdomen and abdominal distention are almost always present. Diarrhea is occasionally a symptom, gross blood in the feces is infrequent. The finding of a firm tumor in the rectovaginal septum or of tender palpable nodules, plus the palpation of uterine fibroids and bilateral ovarian cysts, is suggestive of endometriosis. The treatment is surgical, consisting usually of panhysterectomy, with or without temporary colostomy, as is deemed necessary. For a younger woman, with a discrete endometrioma of the ileum or of the sigmoid causing obstruction, resection of the intestine without oophorectomy is indicated. Ileal obstruction usually is due to kinking caused by the endometriosis, while the obstruction in the sigmoid and in the lower part of the intestine more often is due to an impingement of the endometrioma into the lumen of the intestine.

⁶⁴³ Pemberton, J. deJ., Comfort, M. W., Fair, E., and Zaslow, J. *Intestinal Lipodystrophy (Whipple's Disease)*, Surg, Gynec & Obst **85**:85, 1947.

⁶⁴⁴ McGuff, P. *Endometriosis as a Cause of Obstruction of the Intestine*, Proc Staff Meet, Mayo Clin **23**:215, 1948. McGuff, P., Dockerty, M. B., Waugh, J. M., and Randall, L. M. *Endometriosis as a Cause of Intestinal Obstruction*, Surg, Gynec & Obst **86**:273, 1948.

Sutler⁶⁴⁵ reports involvement of the intestinal tract in 35 of 848 cases of endometriosis (4.13 per cent). Of these, the appendix was affected in 25, the rectosigmoid, in 9, and the ileum, in 1. Involvement of the bowel occasionally simulates malignancy. Intussusception occurred in a woman of 23⁶⁴⁶, early obstruction, in a housewife of 44⁶⁴⁷.

Intussusception—Among 129 cases of intestinal invagination, 28 were in children from 3 to 15⁶⁴⁸. Failure to recognize acute intussusception is the chief cause of death⁶⁴⁹. Spontaneous passage of blood was the initial manifestation in only 4 of 100 cases. Vomiting and spasmodic pain are frequent early symptoms.

Dennis⁶⁵⁰ performed 8 successful resections in children. McLaughlin⁶⁵¹ concludes that recovery in children under 1 year is unusual.

Two cases are reported of spontaneous chronic intussusception of the ileum into the cecum in adults, both relieved by barium sulfate enemas⁶⁵². The onset of symptoms was acute and was followed with chronic periodic abdominal pain and diarrhea. One patient underwent an appendectomy three months before the diagnosis of intussusception was made. In 1 case, intussusception was due to a solid tumor of aberrant pancreatic tissue, 15 cm from the ileocecal valve⁶⁵³, multiple intussusception of traumatic origin is reported⁶⁵⁴.

Experimental intussusception in dogs was reduced by 3 feet (91 cm) of saline hydrostatic pressure when the process was of less than thirty-eight hours' duration⁶⁵⁵.

645 Sutler, M. R. *Endometriosis of the Intestinal Tract*, *Surgery* **22** 801, 1947.

646 Southern, E. M. *Aberrant Endometrial Tissue and Intussusception*, *Brit M J* **1** 1178, 1948.

647 Katz, A. B. *Endometriosis of the Ileum*, *Am J Digest Dis* **15** 162, 1948.

648 Duhamel, B. *Les aspects anatomo-cliniques des invaginations intestinales et en particulier des invaginations du colon transverse chez les infants de plus de trois ans*, *Presse med* **55** 499, 1947.

649 Morrison, B., and Court, D. *Acute Intussusception in Childhood*, *Brit M J* **1** 776, 1948.

650 Dennis, C. *Resection and Primary Anastomosis in the Treatment of Gangrenous or Non-Reducible Intussusceptions in Children*, *Ann Surg* **126** 788, 1947.

651 McLaughlin, C. W., Jr. *Surgical Management of Irreducible Intussusception*, *Arch Surg* **56** 48 (Jan) 1948.

652 Hansen, P. B. *On Spontaneous Chronic Intestinal Invagination in Adults*, *Acta radiol* **28** 115, 1947.

653 Bosworth, B. M., and Stein, H. D. *Intussusception in Adults*, *Am J Surg* **74** 801, 1947.

654 Falor, W. H. *Multiple Intussusceptions, Direct and Retrograde, of Traumatic Origin*, *Ann Surg* **127** 730, 1948.

655 Ravitch, M. M., and McCune, R. M., Jr. *Reduction of Intussusception by Hydrostatic Pressure*, *Bull Johns Hopkins Hosp* **82** 550, 1948.

Intestinal Obstruction—Case⁶⁵⁶ advocates the use of umbrathor,[®] an aqueous preparation of thorium dioxide, for the roentgenologic examination of patients with acute or chronic obstruction. The potential danger from the use of barium sulfate is avoided, the material effectively aids in determining the site and extent of the lesion.

Osgood⁶⁵⁷ presents a detailed and instructive discussion of the roentgenologic features of intestinal obstruction, with particular reference to the use of the Miller-Abbott tube. Roentgenographic findings were conclusive in 94 of 100 cases⁶⁵⁸. Adhesions were responsible for 78 per cent of the obstructions. The importance of a "scout film," to be followed by special views only as necessary, is stressed. Frimann-Dahl⁶⁵⁹ discusses, in considerable detail, the roentgenologic features of mechanical and paralytic ileus. Repeated examination is advocated in cases in which the roentgenologic findings are inconclusive.

Six cases of adynamic ileus are reported by Leithauser⁶⁶⁰. The distention was not controlled by mechanical decompression or by the administration of neostigmine methylsulfate U S P (prostigmin methylsulfate[®]) but seemed to respond dramatically to the administration of thiamine hydrochloride and vitamin B complex. It seems to the reviewers that more evidence is needed before the concept of nutritional ileus can be accepted.

Zuelzer and Wilson⁶⁶¹ describe 11 cases in which the clinical picture was that of acute, recurrent or chronic intestinal obstruction, for which no mechanical cause was demonstrable. Autopsy in 5 cases revealed an absence of the myenteric plexus in the distal portion of the intestinal tract, which correlated to a fair degree with the level of "obstruction."

Two interesting cases are reported in which torsion of the small bowel occurred through congenital mesenteric defects⁶⁶², the patients in both cases died of shock. A total of 97 similar cases have been described in the literature, the mortality rate among 73 of the group

656 Case, J. T. Umbrathor as a Substitute for Barium in the Roentgen Study of Acute Intestinal Obstruction, *Am J Roentgenol* **58**:422, 1947.

657 Osgood, E. C. The Role of the Radiologist in the Management of Patients with Intestinal Obstruction, with Special Reference to the Use of the Miller-Abbott Tube, *Radiology* **49**:529, 1947.

658 Spencer, J., and Thaxter, L. T. Acute Obstruction of the Small Bowel, *Radiology* **49**:611, 1947.

659 Frimann-Dahl, J. Roentgenological Examinations of Ileus, *Acta radiol* **28**:331, 1947.

660 Leithauser, D. J. Atypical Adynamic Ileus Apparently Caused by Nutritional (Thiamine Chloride) Deficiency, *Surg, Gynec & Obst* **86**:543, 1948.

661 Zuelzer, W. W., and Wilson, J. L. Functional Intestinal Obstruction on a Congenital Neurogenic Basis in Infancy, *Am J Dis Child* **75**:40 (Jan) 1948.

662 Vuori, E. E. Two Cases of Incarceration in a Defect in the Mesentery of the Small Intestine, *Acta chir Scandinav* **95**:541, 1947.

was 33 per cent De Nicola⁶⁶³ describes obstruction produced by multiple thrombi in the small radicles of the mesenteric veins Spackman⁶⁶⁴ emphasizes the danger of irradiation injury to the small bowel and the sigmoid in the treatment of cancer of the uterus and cervix Intraperitoneal adhesions, resulting from the injection treatment of an inguinal hernia, caused fatal obstruction⁶⁶⁵ Obstruction complicated a seven month pregnancy⁶⁶⁶ Ileus followed cesarean section⁶⁶⁷ A schizophrenic patient recovered uneventfully after the surgical removal of two teaspoons, three toothbrushes, two nails, wool fibers, a wood splinter and a piece of moleskin cloth, in addition to the appendix, from the gastrointestinal tract⁶⁶⁸

Patients have survived the removal of bezoars,⁶⁶⁹ orange pulp⁶⁷⁰ and accumulations of ascaris⁶⁷¹

Interesting cases of gallstone ileus are described by Lace,⁶⁷² Meiselas,⁶⁷³ Kapel,⁶⁷⁴ and Minty and others⁶⁷⁵

Macnab,⁶⁷⁶ and Cole⁶⁷⁷ review the classification, pathology, symptomatology and treatment of acute intestinal obstruction The decreasing mortality rate is attributed to early diagnosis, intelligent use of gastrointestinal decompression, careful attention to fluid, electrolyte and protein balance and improved operative technic The importance of

663 De Nicola, R R Unusual Findings in the Ileocecal, Appendiceal Region, *Northwest Med* **46** 519, 1947

664 Spackman, J G Obstructive Lesions of the Small Intestine and Sigmoid Due to Irradiation, *Ann Surg* **127** 121, 1948

665 Lawrence, K B Fatal Intestinal Obstruction Following Injection Treatment of an Inguinal Hernia, *New England J Med* **238** 397, 1948

666 Siegel, S A, and Pleshette, N Intestinal Obstruction Complicating Pregnancy, *New York State J Med* **48** 1264, 1948

667 Neff, G Ileus nach Schnittentbindung, *Schweiz med Wchnschr* **77** 755, 1947

668 Schantz, B A, and Kamil, R S Mechanical Intestinal Obstruction, *New York State J Med* **47** 2605, 1947

669 Watt, C H, and Harner, J W Bezoars Causing Acute Intestinal Obstruction, *Ann Surg* **126** 56, 1947

670 Baumeister, C F, and Darling, D D Acute Intestinal Obstruction Due to Orange Pulp Bezoar, *Ann Surg* **126** 251, 1947

671 Verhaege, E Acute Intestinal Obstruction Caused by Ascaris, *Lille chir* **2** 112, 1947

672 Lace, T Gallstone Ileus, *Am J Surg* **74** 86, 1947

673 Meiselas, D A A Case of Gallstone Ileus, *Rev Gastroenterol* **14** 857, 1947

674 Kapel, O Operative Treatment of Gallstone Ileus Without Enterostomy, *Acta chir Scandinav* **95** 54, 1947

675 Minty, E W, McHaffie, O L, and Wells, A H Diagnostic Case Study, *Minnesota Med* **31** 656, 1948

676 Macnab, D S Acute Intestinal Obstruction, *Canad M A J* **57** 371, 1947

677 Cole, W H Intestinal Obstructions, *Canad M A J* **58** 241, 1948

correcting fluid and electrolyte imbalance and hypoproteinemia in acute obstruction of the small bowel is again emphasized⁶⁷⁸ Crile⁶⁷⁹ also stresses the importance of intubation with the Miller-Abbott or Harris tube and the restoration of fluid and electrolyte balance Baumgartner⁶⁸⁰ states that delay in operation may be attributed to the "calming influence of indwelling siphonage both on the patient and on the surgeon"

Tendler and his associates⁶⁸¹ report an over-all mortality of 26 per cent The elapsed time factor is apparently of prime importance, since more than 50 per cent of the patients who died had come to the hospital four days or more after the onset of symptoms, whereas of 555 patients admitted within twenty-four hours after the onset of symptoms, only 10.5 per cent died

Skjold⁶⁸² reports a mortality rate of 27 per cent in 148 consecutive cases Persistent postoperative paralytic ileus was relieved by cecostomy⁶⁸³

Viability of Strangulated Bowel—Laufman and Method⁶⁸⁴ studied the role of vascular spasm in the recovery of strangulated bowel Release of strangulation of the arterial type was followed by reactive hyperemia and then by a phase of vasospasm Release of viable strangulation of the venous type was followed by a slow rise in temperature to a control level Release of strangulation in nonviable bowel resulted in "poor" temperature response Administration of papaverine hydrochloride, warm packs, oxygen inhalation, and mesenteric injections with procaine hydrochloride U S P (novocain®) were of value in releasing residual vasospasm Lichtenstein⁶⁸⁵ states that he regards observation of change in the color of the bowel concomitantly with the inhalation of 100 per cent oxygen as one of the most delicate tests for viability of the bowel The immediate transition of a dusky colored bowel to a bright pink is an indication that blood is circulating through the wall of the bowel, and viability is assured

678 Efskind, L A Clinical Study of the Hematological Changes in Acute Obstruction of the Small Intestine, *Acta chir Scandinav* **95** 519, 1947

679 Crile, G, Jr Medical Aspects of Intestinal Obstruction, *M Clin North America* **32** 373, 1948

680 Baumgartner, C J Survey of Intestinal Obstruction, *Arch Surg* **55** 607 (Nov) 1947

681 Tendler, M J, Streeter, A N, and Cartwright, R S Acute Intestinal Obstruction, *South Surgeon* **13** 551, 1947

682 Skjold, A C Bowel Obstruction, *Minnesota Med* **31** 52, 1948

683 Leiter, H E, and Lyons, A S Cecostomy for Prolonged Chronic Ileus, *J Mt Sinai Hosp* **14** 934, 1948

684 Laufman, H, and Method, H The Role of Vascular Spasm in Recovery of Strangulated Intestine, *Surg, Gynec & Obst* **85** 675, 1947

685 Lichtenstein, M E Tests for Determining the Viability of Strangulated Bowel, *J A M A* **135** 221 (Sept 27) 1947

Analysis of 336 cases, with particular reference to features suggesting the ultimate fate of strangulated bowel, indicated that the risk of subsequent gangrene increased with the length of the bowel involved ⁶⁸⁶ Among 216 cases of replacement in which the color of the bowel was normal, the mortality was 97 per cent, as compared with 30 per cent in 20 cases in which the bowel was discolored. The presence of muscular contractions in the bowel and of pulsations in the mesenteric vessels was associated with a more favorable prognosis.

Intestinal Intubation—Various improvements in the type of tube used and in the technic of intubation are described by Honor and Smathers ⁶⁸⁷ Kaslow ⁶⁸⁸ and Wild ⁶⁸⁹

Harris and Gordon ⁶⁹⁰ evaluate 100 intubations of the small bowel in 86 cases of distention or obstruction or both, utilizing a single lumen, mercury-weighted intestinal tube. This type of therapy was effective in 41 cases, without recourse to surgical intervention. In 59 instances, some type of operative procedure was performed as primary therapy. Complications included coiling of the tube in the stomach, failure of the tube to pass the pylorus, inability to withdraw the tube and rupture of the bag. The principal indication for intestinal intubation is distention of the small bowel, associated with simple adhesive obstructions or with certain medical conditions, it should never be used as primary treatment for strangulation of the small bowel or for obstruction of the colon. Herrera and his associates ⁶⁹¹ state that the Harris tube possesses the advantages of easier passage through the pylorus, a larger single lumen and smaller total diameter. Cantor and his co-workers ⁶⁹² state that the balloons of intestinal decompression tubes are permeable to gases, particularly carbon dioxide and hydrogen sulfide.

Berger and Achs ⁶⁹³ report a case in which perforation of the small intestine occurred after prolonged intubation, the patient recovered.

686 Viability of Strangulated Bowel. Interim Report of Surgical Subcommittee of the Clinical Research Committee of the Public Health Department of the London County Council, *Brit M J* **1** 43, 1948.

687 Honor, W. H., and Smathers, H. M. A Double-Lumened Plastic Tube for Intestinal Intubation, *Arch Surg* **55** 498 (Oct.) 1947.

688 Kaslow, A. L. A New Material and Tube Design in Gastrointestinal Intubation, *Surgery* **23** 293, 1948.

689 Wild, J. H. The Stomach as a Cause of Difficulty in Intubating the Human Duodenum, *Surgery* **24** 70, 1948.

690 Harris, F. I., and Gordon, M. Intestinal Intubation in Small Bowel Distension and Obstruction, *Surg, Gynec & Obst* **86** 647, 1948.

691 Herrera, R. E., Millet, J. B., and Lawrence, G. H. A Report on the Use of the Harris Tube, *Surg, Gynec & Obst* **85** 604, 1947.

692 Cantor, M. D., Phelps, E. R., and Esling, R. H. Effect of Intestinal Gases upon Balloons of Intestinal Decompression Tubes, *Am J Surg* **75** 441, 1948.

693 Berger, L., and Achs, S. Perforation of Small Intestine by Miller-Abbott Tube, *Surgery* **22** 648, 1947.

Intubation resulted in intussusception in 1 instance⁶⁹⁴ Brenizer⁶⁹⁵ reports spontaneous coiling and knotting of a tube in the jejunum, proximal to an obstructing adhesion

Redundant Postoperative Segments—Black and McEachern⁶⁹⁶ call attention to the potential hazards associated with the inverted end of the proximal segment of bowel, following division of the bowel and side to side anastomoses, they are dilatation, hypertrophy, ulceration and perforation They are largely preventable by avoiding redundant segments of the proximal end

Leakage from Enterostomy—Strelinger⁶⁹⁷ describes an appliance for preventing leakage from a gastrostomy or enterostomy wound

Vascular Disease—Cunningham⁶⁹⁸ concludes that in malignant hypertension, severe vascular changes are noted in the gastrointestinal tract with great frequency (the site is second only to the kidney in incidence and severity), whereas in "benign" hypertension, severe arteriolar lesions are much less common Periarteritis nodosa may be associated with ulcerative enteritis and perforation⁶⁹⁹

Scleroderma—Involvement of the jejunum and ileum is described.⁷⁰⁰

Mesenteric Thrombosis—In a case in which massive resection was necessitated by mesenteric thrombosis, approximately 14 inches (36 cm) of jejunum remained⁷⁰¹ The patient survived, but poor fat digestion was evident, with frequent stools, a low serum cholesterol level and deficient absorption of calcium Carbohydrate and proteins were well utilized A similar case is described by Berman and others⁷⁰²

694 Warren, K W, and Cattell, R B Stenosis of the Intestine After Strangulated Hernia with Fatal Complication Following Intestinal Intubation, *Am J Surg* **75** 729, 1948

695 Brenizer, A G, Jr Unusual Complication of Intestinal Intubation, *New England J Med* **238**:279, 1948

696 Black, B M, and McEachern, C G Redundant Blind Segments of Intestine Following Side-To-Side Anastomosis with Division of the Bowel, *Surg, Gynec & Obst* **86**:177, 1948

697 Strelinger, A An Appliance for Preventing Leakage of Gastrostomy and Enterostomy, *Am J Digest Dis* **15** 14, 1948

698 Cunningham, G J Intestinal Lesions in Malignant Hypertension, *Brit M J* **1** 1075, 1948

699 Berris, R F, Sawyer, K C, and Lubchenco, A E Periarteritis Nodosa with Ulcerative Enteritis and Perforation, *Rocky Mountain M J* **45**:394, 1948

700 Brenner, A J Scleroderma with Gastrointestinal Involvement, *Rev Gastroenterol* **14** 869, 1947

701 Cogswell, H D Massive Resection of the Small Intestine, *Ann Surg* **127** 377, 1948

702 Berman, J K, Brown, H M, Foster, R T, and Grisell, T L Massive Resection of the Intestine, *J A M A* **135**:918 (Dec 6) 1947

Another instance occurred after resection of a carcinoma of the sigmoid⁷⁰³ The subject is reviewed by Debeyre⁷⁰⁴

Perforation, Traumatic Resection and Foreign Bodies—According to Sampson and Stauffer,⁷⁰⁵ the term "subcutaneous rupture of the small intestine" designates a severance of the continuity of the bowel beneath an intact abdominal wall Two cases are reported Perforation of the jejunum may occur after apparently minor trauma⁷⁰⁶ Nine perforations of the jejunum and ileum were observed at autopsy in the case of a sailor exposed to the blast of an explosion⁷⁰⁷ Complete resection of a 12 inch (30 cm) segment of ileum, without penetration of the abdominal wall, occurred in the case of a patient run over by a coal cart⁷⁰⁸ An unusual case of transection of the terminal ileum by an adhesive band is reported⁷⁰⁹ Obstruction of the small bowel had occurred approximately four months after appendectomy Operation was performed eight days after the initial signs of obstruction, only a few hours after initial evidence of perforation of the bowel, but death ensued In another case,⁷¹⁰ in which evisceration occurred subsequent to gastric resection, a jejunal fistula developed

Snodgrass⁷¹¹ reviews the subject of swallowed foreign bodies and presents interesting case reports He concludes that foreign bodies generally cause little trouble unless arrested at one of the angles of the intestinal tract, the ileocecal region is the most common site of perforation A patient was found to have a perforation of the ileum caused by a chicken bone, with inflammation and obstruction of bowel loops contained in a ventral hernia⁷¹²

703 Saltzstein, H C. Mesenteric Thrombosis of Lower Ileum Following Resection of the Sigmoid Colon for Carcinoma, *Am J Surg* **75** 854, 1948

704 Debeyre, J. Infarctus intestinal, *Presse med* **56** 424-D (June 16, supp) 1948

705 Sampson, D A, and Stauffer, H M. Rupture of Small Intestine Complicating Injury of Pelvis, *Radiology* **49** 80, 1947

706 Mortensen, J D. Perforation of Jejunum Due to Minor and Obscure Trauma, with Postoperative Escherichia Coli Peritonitis and Wound Infection Treated with Sulfathiazole and Streptomycin, *Northwest Med* **46** 523, 1947

707 Fink, H. Intestinal Perforation Resulting from Atmospheric Blast, *U S Nav M Bull* **47** 884, 1947

708 Teng, P. Complete Traumatic Resection of Ileum without Penetration of the Abdominal Wall, *West J Surg* **56** viii, 1948

709 Cameron, J A. Transection of Ileum by a Band, *Canad M A J* **57** 581, 1947

710 Joseph, E G. High Intestinal Fistula and Its Treatment by the Use of a Pauls Tube, *Am J Surg* **75** 640, 1948

711 Snodgrass, T J. Foreign Bodies in the Intestinal Tract, *Arch Surg* **55** 441 (Oct) 1947

712 Kilbourne, B C. Perforation of Ileum by Ingested Chicken Bone Complicating Ventral Hernia, *Ann Surg* **127** 1226, 1948

Benign and Malignant Tumors—As reviewed by Root,⁷¹³ the most important roentgenologic signs of benign or malignant tumors are localized deformity, obliteration of the mucosal pattern, obstruction and ulceration

Unusual cases include examples of diffuse polyposis,⁷¹⁴ intussusception produced by a pedunculated lipoma,⁷¹⁵ a large myoma producing intestinal obstruction by compressing the pelvic colon at the brim of the pelvis,⁷¹⁶ and a fibroleiomyoma.⁷¹⁷

Hansen⁷¹⁸ states that hemangiomas are among the rarest of tumors of the small bowel, only 66 cases having been reported in the literature since 1860. Microscopically, hemangiomas fall into three types: (a) simple, consisting of newly formed capillaries; (b) cavernous, consisting of large, blood-filled spaces; and (c) combined, a combination of the first two. Grossly, the tumors fall into four classes: (1) multiple phlebectasia; (2) cavernous hemangioma; (3) simple capillary hemangioma; and (4) localized angiomatosis. The symptoms may be those of hemorrhage and obstruction. Associated angiomatosis of the skin may be present. Cavernous hemangiomas may contain phleboliths demonstrable by roentgenologic examination.

A neurinoma, the size of a man's head,⁷¹⁹ and a neurofibrosarcoma, in a patient with neurofibromatosis (von Recklinghausen's disease),⁷²⁰ are reported.

Of 62 tumors of the small bowel, 44 were benign.⁷²¹ Two of these caused symptoms because of intussusception. Twelve neoplasms were found to be carcinomas. The chief symptoms in the cases of malignant growths were abdominal pain, vomiting, melena, diarrhea and weakness. The tumors were palpable in 9 cases. A lesion of the small bowel

713 Root, J. C. Roentgenologic Diagnosis of Tumors of the Small Intestine, *M. Clin. North America* **32** 436, 1948.

714 Manfredi, F. J., and Vivoli, D. Poliposis difusa o generalizada del intestino delgado, *Rev. Asoc. med. argent.* **61** 632, 1947.

715 Sherry, L. B. Lipoma of the Ileum Causing Ileo-Ileal Intussusception in an Adult, *West J. Surg.* **55** 604, 1947. Lawler, R. H., Ragins, A. B., and Silverstein, J. Submucous Lipofibroma of the Ileum, *Am. J. Surg.* **74** 820, 1947.

716 Cookson, C. C. Myoma of the Small Intestine Causing Intestinal Obstruction, *Lancet* **2** 280, 1947.

717 Froelich, A., and Gepts, W. Fibroleiomyome du jejunum, *Acta gastroenterol. belg.* **10** 515, 1947.

718 Hansen, P. S. Hemangioma of the Small Intestine, *Am. J. Clin. Path.* **18** 14, 1948.

719 Moller, W. Solitary Neurinoma of the Small Intestine, *Acta chir. Scandinav.* **96** 1, 1947.

720 Clay, A. G. H. Neurofibrosarcoma of the Small Intestine Associated with Von Recklinghausen's Disease, *Post-Grad. M. J.* **23** 572, 1947.

721 Dundon, C. C. Primary Tumors of the Small Intestine, *Am. J. Roentgenol.* **59** 492, 1948.

was demonstrated in 8 of 11 cases in which roentgenologic examination was made. The average duration of life in 12 cases in which operation was performed was eight and one-half months. In 5 cases, a typical history was not given, the lesion caused no obstruction or bleeding, and no abdominal mass could be palpated. Among 52 cases of malignant tumors of the small intestine,⁷²² there were 21 carcinomas of the duodenum and 1 lymphosarcoma, 17 per cent of these tumors were in the supra-ampullary portion, 61 per cent in the periampullary portion and 22 per cent in the infra-ampullary portion.

Weinbaum⁷²³ reviews 14 cases of primary malignant tumors, including 4 adenocarcinomas of the duodenum, 1 of the jejunum, 1 leiomyosarcoma of the jejunum, 1 lymphocytic lymphoma of the jejunum, 1 carcinoma of the jejunoileal junction, 3 carcinomas of the ileum, 2 carcinoids of the ileum and 1 reticulum cell lymphoblastoma of the ileum. Of 19 cases of tumors described by Eckel,⁷²⁴ 7 lesions were benign and 12, malignant. Additional cases are reported by Delano⁷²⁵ and Lippert.⁷²⁶ Carcinoids and similar tumors are described by several other authors.⁷²⁷

Rabinovitch and others⁷²⁸ report 9 cases of sarcoma of the small bowel, in 5 of which the lesion was in the colon and in 1 in the rectum. The diagnosis was not made before operation, and in many cases not until the histologic examination. Other interesting cases are described.⁷²⁹

(To Be Continued)

722 Doub, H. P. Malignant Tumors of the Small Intestine, *Radiology* **49** 441, 1947.

723 Weinbaum, J. A. Primary Malignant Tumors of the Small Intestine, *Rev Gastroenterol* **14** 478, 1947.

724 Eckel, J. H. Primary Tumors of the Jejunum and Ileum, *Surgery* **23** 467, 1948.

725 Delano, P. Tumors of the Small Intestine, *Am J Roentgenol* **59** 685, 1948.

726 Lippert, R. M., Potozky, H., and Nelson, L. E. Carcinoma of the Terminal Ileum. A Cancer Study, *J South Carolina M A* **44** 123, 1948.

727 D'Albora, J. B., and Ingegno, A. P. Carcinoid Tumors of the Small Bowel, *Gastroenterology* **10** 310, 1948. Fraenkel, G. J. Carcinoid Causing Obstruction, *Lancet* **1** 404, 1948. Hoffman, J. M. Tumor Intussusception, *Northwest Med* **46** 950, 1947.

728 Rabinovitch, J., Grayzel, D. M., Sawyer, A. J., and Pines, B. Sarcomas of the Small and Large Intestine, *Surg, Gynec & Obst* **85** 333, 1947.

729 Salvesen, H. A. Symptomatic Sprue Due to Reticulosarcomatosis of the Small Intestine and the Mesentery Glands, *Gastroenterologia* **73** 166, 1948. Carnes, E. H. Reticulum Cell Sarcoma of the Ileum, *Am J Surg* **74** 49, 1947. Bastrup-Madsen, P. Plasmocytoma of Small Intestine, *Nord med* **35** 1919, 1947. Donovan, R. E. Invagination cronica de intestino, por sarcoma fibroblastico (2 casos), *Bol y trab, Acad argent de cir* **31** 607, 1947. Badia, P. D. Primary Hodgkins Sarcoma of the Jejunum with Perforation. Resection and Radiotherapy, *Am J Surg* **59** 577, 1947.

News and Comment

GENERAL NEWS

Postgraduate Courses at University of California—The University of California Medical School, San Francisco, will hold a postgraduate course on physics in radiation therapy, September 6 through September 9. The course will consist of ten lectures by Dr. Edith H. Quimby, Associate Professor of Radiology, Columbia University, on physics as it pertains to ionizing radiations. Emphasis will be placed on the basic principles and their application to problems of therapy. The course will be of particular interest to radiologists, dermatologists and gynecologists.

The University of California has also scheduled a course in the medical aspects of nuclear energy, to be given from August 29 through September 3. Subjects to be discussed include fission and the chain reaction, the pile and the bomb, principles and applications of radioactive tracers to the medical and biologic sciences, diagnostic applications of artificial radioactivity, treatment of leukemias and allied conditions with radiophosphorus, radioiodine in the treatment of hyperthyroidism and carcinoma of the thyroid, diagnosis and treatment of acute and chronic radiation illnesses, problems of protection associated with the handling of radioactive materials, radiologic hazards associated with large scale release of nuclear energy, evaluation of biologic experiments conducted at Bikini, and genetic effects of ionizing radiation.

Detailed printed programs for these courses may be secured from Dr. Stacy R. Mettler, Professor of Medicine, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

Revised Edition of Motion Picture Reviews Now Available—The Committee on Medical Motion Pictures has completed the first revised edition of the booklet entitled "Reviews of Medical Motion Pictures." It now contains all the film reviews published in *The Journal of the American Medical Association* to Jan. 1, 1949. It also includes a classified table of contents and list of motion pictures available through the Motion Picture Library, American Medical Association.

The purpose of the reviews is to provide a brief description and evaluation of motion pictures which are available to the medical profession. Each film is reviewed and commented on by competent authorities.

Copies are available on request from Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

Annual Meeting of Mississippi Valley Medical Society—The fourteenth annual meeting of the Mississippi Valley Medical Society will be held at the Jefferson Hotel, St. Louis, September 28, 29 and 30, under the presidency of Alphonse McMahon, M.D. The entire program, including some sixty scientific and technical exhibits, is planned to appeal to the general practitioner. No registration fee will be charged. During the course of the meeting, on September 28 and 30, respectively, the American Medical Writers' Association, formerly the Mississippi Valley Medical Editors' Association, and the Missouri chapter of the American Academy of General Practice will hold their annual meetings at the same hotel. Programs of all three meetings may be obtained from Harold Swanberg, M.D., 209-224 W. C. U. Building, Quincy, Ill.

School of Medical Illustration—The first school of medical illustration in the southeastern United States has been opened at the University of Georgia School of Medicine

The courses are designed to equip illustrators for work in all fields of scientific illustration. Since a knowledge of the technics of medical illustration is necessary for the production of exemplary illustrations in various fields of scientific education and publication, special students who wish to apply such technics to a field of classical study other than medicine may be accepted.

Only a limited number of applicants are selected each year for the training. Applications for admission may be addressed to the Registrar, University of Georgia School of Medicine, Augusta, Ga.

Convention of Biological Photographic Association—The nineteenth annual meeting of the Biological Photographic Association, Inc., will be held in Cleveland, September 7 through September 10. The Pre-Convention issue of the *Biological Photographic Association Journal* will include hotel reservation cards as well as more complete details of the convention plans. Entry blanks for the salon may be obtained from Mr. William Stevenson, Mt. Sinai Hospital, 1800 East 105th Street, Cleveland 6. Other information concerning the convention may be secured from its general chairman, Mr. David Lubin, 130 Keats Lane, Berea, O.

Postgraduate Course in Psychiatry and Neurology—A full time postgraduate course of twelve weeks in psychiatry and neurology will be offered at the Langley Porter Clinic, University of California Medical School, San Francisco, August 29 through November 18. The course will be under the chairmanship of Karl M. Bowman, M.D., Professor of Psychiatry, University of California. The fee will be \$200. Program and information may be obtained from Stacy R. Mettler, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

Japanese Medical Journal—The *Japanese Medical Journal*, official organ of the National Institute of Health of Japan, has been recently released. Volume 1, number 1 appeared in February 1948. The magazine is published bimonthly.

The managing editor of the new journal is Hidetake Yaoi. Editorial offices are located at Shiba Shirokane Daimachi, Minato-Ku, Tokyo.

All articles appearing in the February 1948 and April 1948 issues are by Japanese authors and appear in English.

Book Reviews

Twentieth Century Speech and Voice Correction Edited by Emil Froeschels,
M.D. Price, \$6 New York Philosophical Library, Inc., 1948

This volume of twenty-two chapters is a series of essays concerning the various phases of corrective speech training organized for professionals and others interested in remedial measures.

Emil Froeschels, a leader in speech and voice therapy, organized the volume and contributed three of its chapters. Two other chapters are written by physicians. These five chapters deal with the anatomy, physiology and pathology involved in speech and in speech defects. They also describe surgical measures to correct congenital and traumatic lesions. The remaining seventeen chapters are written by sixteen professional speech and voice teachers, trainers and correctionists. The volume is not concerned with training the normal voice but with remedying marked defects.

Considerable space is devoted to aphasia, aphonia, dysphonia and related subjects, with full discussion of their neurogenic background. In line with this, considerable space is devoted to the development and training of the residual ability to hear certain tones present in the great majority of those considered to be totally deaf. The psychologic aspects of these problems are thoroughly discussed as well as the underlying anatomy and physiology.

One chapter is concerned with training the speaking voice and one with training the singing voice. However, the major emphasis of the volume is concerned with the correction of major defects of speech and with teaching those to speak who have never spoken or who have lost the ability to speak. The final chapter is on voice training after total laryngectomy.

Tuberculosis in Childhood Second edition Revised by Henry F. Macauley
Price, \$7 Pp 228 Baltimore Williams & Wilkins Company, 1948

This book can be recommended to the pediatrician and the general practitioner as a good over-all picture of tuberculosis in childhood in all its phases. The successful treatment of tuberculous meningitis with streptomycin deserves more attention in a book appearing in 1948 than the mere statement that the drug shows some promise. The advantage of BCG vaccination of tuberculin-negative young adults as well as the importance of immediate treatment of primary tuberculosis in this age period is particularly emphasized.

Investigations into the Development of the Pituitary and Hereditary Anterior Pituitary Dwarfism in Mice By Torben Francis Copenhagen
Ejnar Munksgaards Forlag, 1944

This monograph by Torben Francis has been translated from the Danish. Its object is to study the development of the adenohypophysis in mice with hereditary anterior pituitary dwarfism. The work of other investigators of the anterior pituitary lobe in the experimental animal and in the human being is reviewed in detail.

In 1929 Snell found dwarfism in a strain of mice. This strain has been studied extensively, particularly with reference to the pituitary gland. Two hundred

fetuses and young of this strain of mice constitute the material for the experimental study. They were killed after the age of 9 fetal days, by which time the anlage of the anterior pituitary lobe is developed, to the age of 12 days after birth, when the dwarf growth manifests itself. In addition, the pituitary glands of older mice which were dwarfs and some which were normal were studied. All the histologic observations on fetuses, immature mice, dwarfs and nondwarfs of the dwarf strain have been compared with those on mice from a strain which has no hereditary disposition to dwarfism.

The technic required to secure the fetuses from the uterus, the method of measurement and the excision and embedding of the pituitary gland are discussed in detail.

The histology and embryology of the adenohypophysis and other endocrine glands of the dwarf mouse from the ninth fetal day to maturity are discussed in great detail. The role played by the different types of cells in the growth of the body is presented clearly, which is a real contribution to the understanding of dwarfism.

This monograph is based on a thorough review of the literature on the anterior pituitary lobe and an extensive embryologic and histologic study of the pituitary of the strain of dwarf mice. The presentation of the material lacks organization and makes the reading difficult. One has the feeling that the author tried too hard to achieve completeness and in so doing sacrificed clarity, which will result in the book's being read less than it should by those who are interested in knowing more of this important and interesting structure of the body.

Pathology Edited by W A D Anderson, M D Price, \$15 Pp 1,453, with 1,183 illustrations St Louis The C V Mosby Company, 1948

This is an excellent new textbook of pathology written by Dr W A D Anderson and thirty-one distinguished collaborators. The organization of the text is conventional. However, the constant emphasis in relating the postmortem findings to antemortem clinical findings and disturbances of function makes the book of more interest than older ones. The effects of radiation and chemical injury, viral, fungus, protozoal and helminthic infections, diseases of the skin, and diseases of the skeletal system receive relatively more attention than in most books on pathology. The extensive bibliographies will be appreciated by graduate students and practitioners. The book has everything required to make it eminently satisfactory for both student and physician. It deserves a wide distribution.

Practical Aspects of Thyroid Disease By George Crile Jr, M D, F A C S Price, \$6 Pp 355, with 101 illustrations Philadelphia W B Saunders Company, 1949

This book is especially valuable because it brings the reader up to date on accepted opinions on diseases of the thyroid gland. The author has avoided long discussions, charts and experimental data and, with a minimum of words, has covered each subject well.

The chapters on basic physiology and pathology clearly explain today's concept of these subjects. Toxic diffuse goiter and toxic nodular goiter are well distinguished with regard to diagnosis and treatment. In many minds, there is confusion regarding the indications for the use of iodine, antithyroid drugs and thyrotropic hormone and for surgical intervention, these are clearly explained and differentiated. The chapter on the use of antithyroid drugs is especially well organized and written.

Four chapters are devoted to the discussion of malignant tumors of the thyroid. The author uses the accepted classification of the common carcinomas of the thyroid, dividing them into papillary and nonpapillary types, and discusses differentially the symptoms, pathologic features and treatment.

The chapter on roentgen therapy and the use of radioactive iodine is primarily a summary of the opinions of other workers in this field and of results of their experiments, together with observations from the author's limited experience. It confirms a conviction that that avenue of therapy, while most fascinating, still must be left to well organized and controlled clinics for further development.

The book is made complete by inclusion of discussions on the symptoms and diagnosis of hyperthyroidism, the technic of thyroidectomy, anesthesia, preoperative and postoperative care, complications, inflammatory conditions and extrathyroid diseases. The reviewer knows of no other single volume which covers the whole subject of thyroid disease so clearly, yet briefly, as does this book.

Thyroid Enlargement and Other Changes Related to the Mineral Content of Drinking Water (with a Note on Goiter Prophylaxis) By Margaret M. Murray, J. A. Ryle, Beatrice W. Simpson and Dagmar C. Wilson. Medical Research Council Memorandum no. 18. Price, 9d. Pp. 39. London: His Majesty's Stationery Office, 1948.

This booklet brings out most of the well known facts about endemic goiter, particularly regarding its etiology and treatment. It reports a survey of adolescents and young adults in counties and towns in various parts of England and Scotland, and of the drinking waters in the same communities, to determine their iodine content and "hardness", findings are correlated with the incidence of endemic goiter.

The authors note that McClendon and Williams, in the United States, found those areas in which the drinking water contained 3 mg or more of iodine per liter to be practically free from goiter. By comparison, in England generally it was found that an iodine content of 5 mg of iodine per liter was the preventive level, this is attributed to the "hardness" of the water. In those regions of England and Scotland where the water was "soft," a level of 3 mg of iodine per liter prevented goiter, as in the United States.

It had previously been observed that a high incidence of goiter existed in those regions where an excess of fluorine was present in the drinking water. Admitting that the problem is complex, the observers state the belief that goiter was absent or minimal in those regions whenever the iodine intake was adequate.

The minimal daily requirement of iodine has never been definitely established, but it is the feeling of these writers as well as of others that even in those regions having water of high iodine content, that source must be supplemented by iodine in the diet to meet minimal requirements.

A parallel is drawn between the incidence of cretinism and deaf-mutism and that of goiter in areas where a deficiency of iodine exists.

Several charts are published which compare the incidence of goiter with the iodine content and the "hardness" of available drinking water in specific counties in England and Scotland, which should be valuable to physicians and health officers.

The authors postulate and fairly convincingly show that the primary cause of endemic goiter is the deficiency of iodine in the available supply of water and foods. They advocate the addition of iodine, in the form of iodized salt, to the diet as the prophylactic treatment.

A History of the Heart and the Circulation By Frederick A Willius, M D, and Thomas J Dry, M A, M B, Ch B, M S in Med Price, \$8 Pp 473, with 160 illustrations Cloth Philadelphia and London W B Saunders Company, 1948

This book deals with the sources from which knowledge of the heart and vascular system arises. It is divided into three main sections. The first section consists of a resume of the chronologic presentation of this subject from 5000 B C to 1925 A D. As this section occupies 225 pages one must realize that it is packed with information. The section mentions the name of the contributor, the subject of his contribution and the date on which the contribution was made. The story progresses rapidly from era to era but contains information about practically everyone who made an important contribution to this subject. A good list of references follows each chapter in this section.

The second section is made up of a series of special biographies. These are short sketches of the lives of the men who the authors believe deserve special mention. The sketches are well done, but this section is sure to provoke some criticism and perhaps a little resentment. The authors have attempted to disarm this criticism in their preface by suggesting that their selection of subjects for the special biographies might not be in agreement with the selection of others. They point out that the achievement of unanimity in this selection would be impossible. This is true. It would seem that the group might well have been discussed in the running account (as indeed they were, briefly) and thus criticism would be avoided. This reviewer wonders at the omission of Vaquez, Heberden, Herrick and Maude Abbott from the list, to mention but a few. There are twenty of these special biographies. They start with Hippocrates and end with Sir Thomas Lewis. Rudolph Matas is the only survivor in the group. Again, a list of references follows each biographic sketch.

The third section is written in outline form and contains a chronologic account of subject matter. Anatomy of the heart and circulation is dealt with chronologically and then aneurysm and related subjects. This is well done.

The book contains no mention of the later surgical operations for heart disease or of the subject of angiocardiology. It is assumed that the authors considered that these subjects were to be discussed as the developments of a later period.

It is noteworthy that so many fundamental contributions to the subject were made by persons who today would not be called "cardiologists." The contributions of physicists, surgeons, physiologists and pediatricians abound. Neurologists are included. Among the internists, a great number were, and considered themselves, general internists and not "cardiologists." Rokitsky and Bright, for instance, achieved greater fame in fields other than that of heart disease. One wonders about the advisability of too sharply limiting a special field of endeavor in medicine.

The authors in the preface point out the possibility of errors' creeping into such a comprehensive work. This is particularly true in the matter of credit. The authors assume that the contribution is always of greater importance than the man who made it. This is true, but the matter of credit is always of importance to the man or to his community or even to his country. For instance, the authors credit C J B Williams, of Great Britain, with the first report of a successful closure of a stab wound of the heart. The credit for this usually goes to a different Williams—Dan Williams, an exceedingly fine Negro surgeon, of Chicago. However, controversial works are always exceedingly interesting and instructive, and this is no exception.

CLINICAL AND BIOCHEMICAL STUDY OF REMISSIONS IN NONSPECIFIC ARTHRITIS

Report of a Case

BENJAMIN H. ARCHER, M.D.
NEW YORK

IT IS WELL known that nonspecific arthritis is a disease which is characterized by relapses and remissions¹. It is also generally accepted that whereas there is no specific curative agent for this disease, there are many measures which hasten remissions in both rheumatoid arthritis and osteoarthritis². As Hench³ recently stated in discussing the use of gold therapy in rheumatoid arthritis, a remission may be obtained by this method in six months in a case in which it otherwise might require six years. Using measures other than chrysotherapy, a smaller percentage of remissions has been reported after the use of such diverse treatments as hyperthermia with typhoid vaccine,⁴ hypervitaminosis with massive doses of activated ergosterol (viosterol).⁵

From the Medical Department and the Pathological Laboratories, Bronx Hospital

1 Archer, B. H. Chronic Nonspecific Arthritis. Etiology and Treatment, with Special Reference to Vaccine Therapy, *J. A. M. A.* **102**:1449 (May 5) 1934

2 (a) Cecil, R. L. Present Day Treatment of Arthritis, *Tr. & Stud., Coll. Physicians, Philadelphia* **15**:7 (April) 1947. (b) Cecil, R. L., and Archer, B. H. Classification and Treatment of Chronic Arthritis, *J. A. M. A.* **87**:741 (Sept. 4) 1926. (c) Holbrook, W. P. Medical Progress. Recent Advances in the Management of Patients with Rheumatoid Arthritis, *New York Med.* (Nov. 7) **4**:17 (April 5) 1948.

3 Hench, P. S. Gold Salts for Rheumatoid Arthritis, editorial, *Ann. Int. Med.* **26**:618 (April) 1947.

4 (a) Hench, P. S., Bauer, W., Boland, E. W., Cram, D. C., Freyberg, R. H., Graham, W., Holbrook, W. P., Lockie, M. L., McEwen, C., Rosenberg, E. F., and Stecher, R. M. Rheumatism and Arthritis. Review of American and English Literature of Recent Years (Ninth Rheumatism Review), *Ann. Int. Med.* **28**:66 (Jan.), 309 (Feb.) 1948. (b) Geiger, F. Fever Therapy in Rheumatoid Arthritis, *M. Clin. North America* **27**:1123 (July) 1943.

5 (a) Norris, G. The Treatment of Arthritis by Electrically Activated Vaporized Ergosterol, *Rheumatism* **3**:103 (July-Sept.) 1947. Magnuson, P. B., McElvenny, R. L., and Logan, C. I. A Clinical Study of One Hundred and Eighty Cases of Arthritis, *J. Michigan M. Soc.* **46**:71 (Jan.) 1947.

bismuth therapy,⁶ low carbohydrate diets,⁷ administration of cinchophen,⁸ starvation,⁹ administration of streptococcus vaccine,¹⁰ administration of foreign protein,¹¹ bee venom therapy¹² and even anesthesia¹³

Of striking significance is the fact that the highest percentage of remissions thus far observed has not followed therapy at all, but has occurred in cases of arthritis in which the patients became pregnant or jaundice developed¹⁴ In 1880, Pletzer¹⁵ reported the case of a patient with "hydrarthrosis," who was helped by pregnancy, attacks ceased and remained absent during pregnancy The arthritis recurred and was relieved again after four months, when symptoms of toxic diffuse goiter appeared In 1890, Garrod¹⁵ commented regarding the relation of pregnancy to "arthritis deformans" (including rheumatoid arthritis and osteoarthritis) "It is curious to observe that the occurrence of pregnancy appears to exert opposite influences in different cases, in some cases accelerating the progress of the malady, in others acting as a temporary check on its development" Other writers have mentioned this relation, but Hench¹⁴ was the first to stress its importance He observed 22 women with arthritis, who had had thirty-seven pregnancies, and found that 20 of the 22 had experienced striking relief after one to three months of pregnancy There was a sharp relapse in many of these cases about one month after delivery More recently, Holbrook,^{2c}

6 Douthwaite, A H Treatment of Rheumatoid Arthritis with Bismuth, *Brit M J* **2** 276 (Aug 26) 1944 Archer, B H, in discussion on Cecil, R L, Treatment of Rheumatoid Arthritis, read before the Bronx County Medical Society, November 20, 1946

7 Pemberton, R Arthritis and Rheumatoid Conditions Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929, pp 246-275

8 (a) Hench, P S Derivatives of Cinchophen and Their Toxicity, *Proc Staff Meet, Mayo Clin* **7** 427 (July 20) 1932, (b) The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, *Ann Int Med* **7** 1278 (April) 1934 This article contains a complete bibliography

9 Hench, P S The Advantage of Hepatic Injury and Jaundice in Certain Conditions, Notably the Rheumatic Diseases, *M Clin North America* **24** 1209 (July) 1940

10 Burbank, R, and Christensen, B E Specific Vaccine Treatment of One Thousand Cases of Chronic Arthritis, with Results and Clinical Observations, *J Bone & Joint Surg* **13** 246 (April) 1931 Wetherby, M, and Clawson, B J Chronic Arthritis, with Special Reference to Intravenous Vaccine Therapy, *Arch Int Med* **49** 303 (Feb) 1932

11 Hench and others,^{4a} p 126

12 Hench and, others,^{4a} p 127

13 Hench⁹

14 Hench^{8a}, b Hench⁹ Complete bibliography appears in Hench,^{8b} Hench,⁹ and Hench and others,^{4a} pp 131-137

15 Cited by Hench, P S Ameliorating Effect of Pregnancy on Chronic Atrophic (Infectious Rheumatoid) Arthritis, Fibrositis, and Intermittent Hydrarthrosis, *Proc Staff Meet, Mayo Clin* **13** 161 (March 16) 1938

reviewing this subject, stated that he was able to collect from the literature, from personal communications and from his own observations, 96 cases of pregnant women with active arthritis. Of this group, 80 (83 per cent) showed pronounced improvement or experienced a remission during pregnancy. In fact, he advised pregnancy for 3 young women who had extremely active and progressive arthritis, resistant to all forms of therapy. All 3 became symptom free before the third month of pregnancy.

According to Aldred-Brown,¹⁶ not every woman with rheumatoid arthritis experiences relief when pregnant, but the majority do. Flynn¹⁷ reported a case in which the condition was refractory to various forms of treatment, including administration of gold salts, but was relieved completely by pregnancy. The arthritis became asymptomatic at the fourth month of gestation, and the remission lasted two and one-half years. Reactivation of the disease occurred six weeks after completion of a second pregnancy. At the time of writing, I have under my care 3 women with rheumatoid arthritis, whose symptoms have disappeared during pregnancy only to recur within two to four weeks after delivery. One of these patients is of special interest. She has had three pregnancies and has had a remission during each pregnancy. The joint symptoms have recurred soon after each delivery. An anonymous writer¹⁸ reported an unusual case of this type in *The Journal of the American Medical Association*. The patient was a woman suffering with chronic arthritis, who had had nine pregnancies. With each pregnancy she had had a remission of the joint disease. In this connection, the observation of Sclater¹⁹ takes on significance. He studied 388 cases of rheumatoid arthritis with this factor in mind. In none of the cases did the disease manifest itself during pregnancy. On the other hand, the onset of rheumatoid arthritis after pregnancy is fairly common and has been noted by many writers.

In addition to the physiologic changes of pregnancy, which seem to induce a remission in a high percentage of cases of arthritis, the pathologic and biochemical changes of jaundice may be equally efficacious. The jaundice may be of the hepatocellular or of the extrahepatic obstructive type. Hemolytic jaundice, on the other hand, seems to be unassociated with remissions. In the series of 72 cases reported by Hench,^{8b} 59 patients had hepatocellular jaundice and 8 had obstructive jaundice of

¹⁶ Aldred-Brown, G. R. P. *Rheumatic Diseases, Practitioner* **149** 209 (Oct.) 1942.

¹⁷ Flynn, S. E. *Effects of Pregnancy on Chronic Atrophic Arthritis. A Case Report*, U. S. Nav. M. Bull. **40** 170 (Jan.) 1942.

¹⁸ *Arthritis Subsiding During Pregnancy, Queries and Minor Notes*, J. A. M. A. **109** 2161 (Dec. 25) 1937.

¹⁹ Sclater, J. G. *An Analysis of Three Hundred and Eighty-Eight Cases of Rheumatoid Arthritis*, Ann. Rheumat. Dis. **3** 195 (Dec.) 1943.

extrahepatic origin. Apparently both types of jaundice were equally effectual in producing remissions of rheumatoid arthritis. In a recent statement quoted by Holbrook,²⁰ Hench stated, "I have seen only one case of rheumatoid arthritis with a significant jaundice not notably relieved." It is worthy of note that in Hench's series, those patients in whom hemolytic jaundice developed were not benefited by the icterus. It is of further interest that Rawls²⁰ reported articular relief in latent jaundice and that Hench⁹ has also seen that phenomenon in cases of arthritis without visible icterus. These observations are in accord with a recent experience of my own in a case in which there was a remission of long-standing rheumatoid arthritis during an attack of hepatitis without jaundice.

More recently, Holbrook²⁰ stated that he had collected the reports of 84 cases of arthritis in which jaundice had developed. Of this group, pronounced improvement occurred in 54 (64 per cent) after the onset of icterus. I can recall only 1 definite instance of jaundice, during the twenty-five years previous to this report, in over 3,000 cases of chronic arthritis. The case was that of a middle-aged woman with rheumatoid arthritis. She was given cinchophen for one week, and a mild icterus developed. There was a prompt remission of the joint symptoms, which lasted only until the jaundice disappeared. The arthritis then recurred, with even greater severity. Recently a patient with osteoarthritis, who had received gold therapy six years before and had had jaundice of six weeks' duration, came under my care. The patient had noted immediate improvement of the arthritis at that time and had had a remission of the joint symptoms which lasted until three months before I saw her.

Some investigators have made attempts to apply the clinical observation that patients with rheumatoid arthritis have remissions during jaundice and pregnancy. Hench⁹ induced hyperbilirubinemia in arthritic patients by the intravenous injection of bilirubin-dehydrocholic acid (decholin®) mixtures. However, the experiments failed to reproduce the results of spontaneous jaundice. In addition, he gave transfusions of jaundiced blood to 4 arthritic patients, who received one to four transfusions, but no relief was obtained. More recently, Gardner, Stewart and MacCallum²¹ produced hepatitis by inoculating patients with rheumatoid arthritis with serum from patients with toxic hepatitis. In 32 of 312 patients with rheumatoid arthritis inoculated, jaundice developed. During the incubation period no change in the arthritis was noted, but with the appearance of jaundice, dramatic improvement

20 Rawls, W. B. The Relief of Arthritic Symptoms Following Urticaria, *J. A. M. A.* **112** 2509 (June 17) 1939.

21 Gardner, F., Stewart, A., and MacCallum, F. O. The Therapeutic Effect of Induced Jaundice in Rheumatoid Arthritis, *Brit. M. J.* **2** 677 (Nov 17) 1945.

was noted by 18 of the 32 patients, there was a complete remission in 10 cases and a considerable improvement in 8. The authors stated that "experimental hepatitis provides an opportunity of providing a remission under controlled conditions and the possibility of analyzing the mechanism by which it is produced."

While these interesting attempts have been made to produce artificial jaundice, clinical application has also been made of the knowledge that pregnancy improves the condition of patients with arthritis. Because of the striking increase of gonadotropin, pregnandiol and estrogens in pregnant women, these hormones have been given alone and in combination to patients with arthritis. The results have been generally unsatisfactory.²² Some authors have reported favorable results by the use of estrogens in arthritis following the menopause,²³ but no striking remissions have been noted.

Barsi²⁴ stated that dramatic improvement followed transfusions of blood from pregnant women to 28 patients with intractable arthritis. He expressed the belief that some unknown substance, circulating in the blood of gravid women, was responsible for the improvement.

An explanation for the definite remissions in cases of arthritis in which patients become pregnant, or in which jaundice develops, has thus far eluded us. Hench²⁵ stated the belief that there must be a potent common denominator of the two conditions, responsible for the clinical improvement. He assumed that the common denominator might be a biochemical factor which was lacking in rheumatoid arthritis. In fact, all investigations made thus far have been predicated on this hypothesis. Hench was inclined to think that the hyperbilirubinemia of jaundice might be the important factor, but he met with failure in his efforts to produce remissions in cases of arthritis by inducing artificial hyperbilirubinemia. Furthermore, there is no significant increase in the serum bilirubin in pregnancy, it is apparently not the biochemical common denominator.

Because of the fact that cholesterinemia and lipemia are common to both pregnancy and extrahepatic obstructive jaundice, both Bayles²⁵

22 Freyberg, R. H. Treatment of Arthritis with Vitamin and Endocrine Preparations. Emphasis of Their Limited Value, *J. A. M. A.* **110** 1165 (Aug. 8) 1942.

23 (a) Cecil, R. L., and Archer, B. H. Arthritis of the Menopause, *J. A. M. A.* **84** 75 (Jan. 10) 1925. (b) Comroe, B. I. Arthritis and Allied Conditions, ed. 2, Philadelphia, Lea & Febiger, 1941, p. 295.

24 Barsi, I. A New Treatment of Rheumatoid Arthritis, *Brit. M. J.* **2** 252 (Aug. 16) 1947.

25 Bayles, T. B., and Riddell, C. B. Plasma Lipids in Patients with Rheumatoid Arthritis Receiving Gold Salt Therapy and During Pregnancy, *Am. J. M. Sc.* **208** 343 (Sept.) 1944.

and Freyberg²⁶ investigated the cholesterol and lipid fractions in rheumatoid arthritis. They found no evidence of any deficiency of these factors in their cases. I believe it unlikely that an increase in cholesterol plays any role in the remission of arthritis in patients who become pregnant or in whom jaundice develops, for several reasons. 1 As a rule, hypercholesterinemia is not present in jaundice of hepatocellular origin.²⁷ In fact, the value of cholesterol may be low, because of a drop in cholesterol esters. Yet, patients with arthritis do experience remissions with hepatitis. 2 Many untreated diabetic patients with a high cholesterol value in the blood have arthritis. I have observed this combination on numerous occasions. 3 In cases of myxedema with a high cholesterol value in the serum, there are a goodly number of instances of arthritis of the degenerative type.²⁸ 4 As already noted, the blood cholesterol in patients with arthritis is within normal range, there is no deficiency present that an increase in cholesterol theoretically might overcome.²⁸

It is pertinent, at this point, to note that there is no evidence at hand to indicate that nonspecific arthritis is a deficiency disease. All available data, as summarized by Comroe,²⁹ tend to show that the fasting blood sugar, basal metabolism, urea nitrogen, nonprotein nitrogen, plasma carbon dioxide-combining power, alkaline phosphatase, serum bilirubin and serum calcium, as well as the cholesterol and the plasma lipids, are all within normal range in cases of rheumatoid arthritis or osteoarthritis. What is more, there is no convincing evidence at hand that patients with arthritis have a vitamin deficiency.

For years, some students of arthritis have tried to connect rheumatoid arthritis with some vague hepatic deficiency, perhaps with a hepatic dysfunction in the nature of a failure of the detoxifying factors of the liver. "But the idea has been incapable of proof since no significant pathological lesion in the liver has been noted and a few studies with different tests of hepatic function have shown no consistent hepatic insufficiency" (Hench³⁰).

My own studies of hepatic function in nonspecific arthritis were made with the aid of the cephalin flocculation test, the thymol turbidity test and the albumin globulin ratio. The results obtained in 20 cases of

26 Block, W. D., Buchanan, O. H., and Freyberg, R. H. Serum Lipids in Patients with Rheumatoid Arthritis and in Patients with Obstructive Jaundice. A Comparative Study, *Arch Int Med* **68** 18 (July) 1941.

27 Cantarow, A., and Trumper, M. *Clinical Biochemistry*, ed 3, Philadelphia, W. B. Saunders Company, 1945, p. 429.

28 Bayles and Riddell.²⁵ Block, Buchanan and Freyberg.²⁶

29 Comroe,^{23b} p. 92.

30 Hench, P. S., and others. Problem of Rheumatism and Arthritis. Review of American and English Literature for 1938, *Ann Int Med* **13** 1837 (April) 1940.

rheumatoid arthritis and osteoarthritis³¹ bear out the contention of Hench and his co-editors³² that there is no evidence of liver dysfunction in untreated cases of nonspecific arthritis. The cases in which treatment has been given, especially with potentially hepatotoxic drugs, such as gold compounds and bismuth preparations, present another problem and will be discussed later in this paper.

From the foregoing data, it seems valid to infer that at the time of this report there is no known specific biochemical deficiency in nonspecific arthritis which theoretically could be overcome by an overproduction of the factor in jaundice or pregnancy. Indeed, the only definitely known biochemical change in nonspecific arthritis is a tendency, in some cases, to a mild hyperglobulinemia³³. But, inasmuch as this biochemical change is also present in many instances of jaundice, it is not likely to be of any significance as an explanation of remissions in chronic arthritis.

Another hypothesis suggests itself. The improvement noted clinically during pregnancy or jaundice in patients with arthritis may bear no relation at all to a biochemical deficiency in arthritis. The remissions may be the result of some biochemical factor or group of factors common to both pregnancy and jaundice, whose presence in a case of arthritis might prove antagonistic to any further rheumatic activity. In other words, it is definitely conceivable that an increase in the blood iodine, the occurrence of hepatic damage and/or dysfunction, and the presence of ketosis, all of which biochemical changes may occur in jaundice and pregnancy,³⁴ may singly or in combination be the reason for remissions of arthritis in pregnancy and jaundice. What is more, the changes may prove to be the explanation of such remissions as follow therapy with a gold compound and are less frequently observed with other forms of treatment.

*Biochemical Changes in Pregnancy**

Diminished dextrose tolerance, with tendency to urinary sugar
Decreased serum albumin
Increased blood iodine
Increased basal metabolism
Decreased blood nonprotein nitrogen and urea nitrogen
Increased blood cholesterol
Increased plasma fatty acid
Increased plasma phospholipid

31 Archer, B. H. Liver Function Tests in Nonspecific Arthritis, with Special Reference to Hyperglobulinemia, to be published.

32 Hench and others,⁴¹ p. 113.

33 Davis, J. S., Jr. Protein Studies in Atrophic (Rheumatoid) and Hypertrophic Arthritis, *J. Lab. & Clin. Med.* **21** 478 (Feb.) 1936. Comroe,^{23b} p. 92. Archer³¹

34 Cantarow and Trumper,²⁷ pp. 163, 219, 514 and 520.

Decreased serum calcium
 Increased serum phosphatase activity
 Decreased plasma carbon dioxide-combining power, with tendency to ketosis
 Histidine in urine
 Increased gonadotropin, pregnandiol and estrogens

* Modified after Cantarow and Trumper,²⁷ p 569

*Biochemical Changes in Hepatocellular Jaundice**

Diminished dextrose tolerance, with tendency to urinary sugar
 Decreased serum albumin
 Increased serum globulin
 Increased blood bilirubin
 Increased blood iodine
 Excessive urinary urobilin and bilirubin
 Decreased plasma prothrombin
 Tendency to decreased plasma urea nitrogen
 Impaired hippuric acid synthesis
 Impaired sulfobromophthalein excretion
 Positive reaction to cephalin flocculation test
 Positive value for thymol turbidity test
 Lowered blood chloride content
 Increased plasma fatty acid
 Tyrosin in urine

* Modified after Cantarow and Trumper,²⁷ p 572

Biochemical Changes in Extrahepatic Obstructive Jaundice †

Diminished dextrose tolerance, with tendency to urinary sugar
 Decreased serum albumin
 Increased blood bilirubin
 Increased urinary bilirubin
 Increased blood iodine
 Decreased plasma prothrombin
 Increased blood cholesterol
 Increased blood fatty acid
 Decreased blood calcium
 Increased serum phosphatase activity
 Tendency to impaired sulfobromophthalein excretion
 Variable urinary urobilin

* Modified after Cantarow and Trumper,²⁷ p 572

Biochemical Changes Common to Hepatic Jaundice, Extrahepatic Obstructive Jaundice and Pregnancy

Diminished dextrose tolerance
 Tendency to urinary sugar
 Tendency to blood and urinary amino acids (histidine in pregnancy, tyrosine in hepatic jaundice)
 Decreased serum albumin
 Increased plasma fatty acid
 Increased blood iodine

It is worthy of note that the six biochemical changes common to the three conditions are, for the most part, directly related to hepatic damage and/or dysfunction

On the other hand, the elevation of the blood iodine level is of special interest. It is consistent with the known fact that the basal metabolic rate is increased in pregnancy³⁵ and may, at times, be elevated in hepatocellular and obstructive extrahepatic jaundice.³⁶ The increased blood iodine, reported by many observers to be present in both forms of jaundice, tends to bespeak an increased basal metabolic rate in these conditions.³⁷ However, the evidence at hand is against any consistently elevated basal metabolic rate in parenchymatous liver disease.³⁸ It is only the occasional patient who shows an elevated rate, and even then there is no evidence to prove that the increase in the metabolic rate is the result of hyperthyroidism.

Of course, the presence of increased blood iodine in both pregnancy and jaundice may have a different significance. It is conceivable that the blood iodine is low in nonspecific arthritis and that the elevated blood iodine level in the two conditions which produce remissions in arthritis may compensate for this deficiency. While we have no figures for the blood iodine level in nonspecific arthritis, the fact that my clinical attempts to saturate these patients with massive doses of iodine have failed completely to help the joint symptoms is against the assumption that the level is low. Indeed, most patients were unable to tolerate large doses (30 minims daily [1.9 cc]) of strong iodine solution U. S. P. (Lugol's solution), as the drug seemed to increase the articular pains.

As already noted, the other biochemical changes which are common to pregnancy and jaundice are those related to hepatic damage and/or dysfunction. The evidence of impairment of hepatic function in pregnancy is supported by many authorities. DeLee and Greenhill,³⁹ discussing hepatic changes in the latter months of pregnancy, state

The liver is enlarged and hyperemic and normally exhibits no histologic changes. There is more bile present, dilatation of the bile passages and ectasis of the central veins. The increased cholesterol content of the bile may explain the frequency of gallstones in child-bearing women. Mechanical factors contribute also. Multinuclear cells presumably from the placenta, even portions of villi, are sometimes found as emboli in the hepatic vessels. The integrity of the

35 Cantarow and Trumper,²⁷ p. 514

36 Archer, B. H. Basal Metabolism in Liver Disease, *Queries and Minor Notes*, J. A. M. A. **138** 1132 (Dec. 11) 1948

37 Salter, W. T. *The Endocrine Function of Iodine*, Cambridge, Mass., Harvard University Press, 1940, p. 86

38 Aub, J. C., and Means, J. H. Basal Metabolism and Specific Dynamic Action of Protein in Liver Disease, *Arch. Int. Med.* **28** 173 (Aug.) 1921

39 DeLee, J. B., and Greenhill, J. P. *Principles and Practice of Obstetrics*, ed. 9, Philadelphia, W. B. Saunders Company, 1947, p. 83

liver is severely taxed by pregnancy and some of its functions do not always meet the demands (1)—The need of the mother and fetus for iron causes much destruction of the erythrocytes which results in an excess of biliary pigments—a cholemia occurs in at least 20 per cent of pregnant women (2)—The glycogenic function is often disturbed as evidenced by hyperglycemia, the rapidity with which administered levulose appears in the urine, and the fact that a brief deprivation of carbohydrate results in acetonuria (3)—The urogenic function is also sub-normal and the liver is frequently unable to arrest all the unreduced albumin absorbed from the intestines (4)—The complicated fat metabolism of the liver is often disturbed, and therefore a tendency to ketonemia exists because the fatty acids are not burned into carbon dioxide and water The same is true of insufficiently aminized proteins and the alkali reserve is thus reduced The alteration of the hepatic cells is most pronounced in eclampsia, hyperemesis and puerperal infection (5)—The requirements placed on the liver as a detoxicating organ are enhanced by pregnancy

In his monograph on diseases of the liver, Lichtman⁴⁰ summarizes his views on the subject

A variety of opinions exist concerning the function of the liver during normal pregnancy A high percentage of abnormalities in liver function tests has been recorded The question has been raised whether this indicates a truly pathologic state It may merely signify overtaxed function of the liver due to increased metabolic demands during pregnancy However, pathologic changes in the liver favor the viewpoint that a significant number of disturbed tests depend on toxic liver damage It is interpreted that the increased functional requirements of pregnancy may lead to a latent hepatopathy

According to Cantarow and Trumper,⁴¹ some degree of impairment of hepatic function, judged by normal standards, may be present in a relatively large percentage of women during pregnancy, particularly during the last few months Additional evidence of hepatic damage in pregnancy has been reported by Wade and Richman⁴² These investigators found that the serum of approximately one fifth of normal pregnant women gave positive results in cephalin flocculation tests at term (The authors listed an even higher figure [one third] but included a 2 plus rating in the cephalin flocculation test as a positive reaction I consider only 3 plus and 4 plus ratings as significant⁴³) In view of the evidence already presented, I am unable to agree with Wade and Richman that positive results in cephalin flocculation tests in pregnancy are "false positives" I am inclined to view positive reactions in late pregnancy as an evidence of impairment of hepatic function

40 Lichtman, S S Diseases of the Liver, Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1942, p 639

41 Cantarow and Trumper,²⁷ p 519

42 Wade, L J, and Richman, E E The Cephalin-Flocculation Test in Mothers and Newborn Infants, *J Lab & Clin Med* **30** 6 (Jan) 1945

43 Kibrick, A C, and Clements, A B A Comparative Study of the Serum Albumin-Globulin Ratio, the Cephalin-Cholesterol Flocculation, and the Thymol Turbidity Tests for Liver Function, *J Lab & Clin Med* **33** 662 (June) 1948

In view of the elevated basal metabolic rate of pregnancy (increased 20 or 30 per cent in some cases), and the known hepatotoxic effect of hyperthyroidism,⁴⁴ there is reason to believe that the elevated metabolic rate of pregnancy may be a competent exciting cause of the hepatic damage and/or dysfunction present. This aspect of the problem has been referred to the obstetric division of the Bronx Hospital for further investigation.

The hepatic damage and dysfunction that occur in hepatocellular jaundice are too well known to require any comment. It is significant that hepatic change with minimal jaundice, or even without jaundice, may produce remissions in arthritis. This fact would tend to suggest the importance of hepatic damage and the relative unimportance of jaundice per se except in so far as jaundice is an indication of hepatic involvement. In this connection, it is well to recall that in cases of hemolytic jaundice in which there is no parenchymatous hepatic damage,⁴⁵ remissions of joint symptoms do not occur. This tends to support the thesis that it is not the jaundice which is the important factor in bringing on remissions in arthritis. It is evident that the biochemical changes in hemolytic icterus are different from those of hepatocellular jaundice and extrahepatic obstructive jaundice.

*Biochemical Changes in Hemolytic Jaundice**

Decreased blood cholesterol
 Decreased plasma phosphatide
 Increased plasma fat
 Increased blood bilirubin
 Negative reaction to direct van den Bergh test
 Variable capacity for bilirubin excretion
 Excessive urinary urobilin
 Increased fecal urobilinogen
 Blood methemoglobin
 Decreased blood volume
 Increased plasma volume

* After Cantarow and Trumper,²⁷ p. 573

It is also fairly clear that the manner in which extrahepatic obstructive jaundice works to produce remissions in arthritis must be due to its secondary effects. It is well known that any long-standing lesion of the biliary tract produces hepatic damage and/or dysfunction.

⁴⁴ Salter,³⁷ pp. 210 and 212. Rowe, A. W. *Endocrine Studies: The Association of Hepatic Dysfunction with Thyroid Failure*, *Endocrinology* **17** 1 (Jan.-Feb.) 1933. Barr, in Cecil, R. L., and Kennedy, F. *Text-Book of Medicine*, Philadelphia, W. B. Saunders Company, 1927, p. 1328. Means, J. *Liver and Toxic Goutre*, *Tr. A. Am. Physicians* **45** 71, 1930.

⁴⁵ Karsner, H. T. *Human Pathology*, Philadelphia, J. B. Lippincott Company, 1926, p. 406.

of varying degree, dependent on the duration and severity of the obstruction ⁴⁶

Inasmuch as the biochemical changes common to extrahepatic jaundice and pregnancy are only those which are also common to hepatocellular and extrahepatic obstructive jaundice, it is reasonable to suppose that it is these factors, rather than those biochemical changes primarily due to biliary obstruction, which play a role in the remission of joint symptoms. Those biochemical changes associated with extrahepatic obstructive jaundice, and not as a rule, with hepatocellular jaundice, such as the increase in the serum alkaline phosphatase or the absence of urobilin in the urine,⁴⁷ are not present in pregnancy. Inasmuch as all three of these conditions, namely, pregnancy, hepatocellular jaundice and obstructive jaundice, are able to bring on remissions in arthritis, it seems logical to suppose that only those biochemical factors which operate in all three conditions are possible potential common denominators of remissions of joint symptoms.

As previously mentioned, remissions may occur in cases of arthritis after the use of a variety of therapeutic agents, in addition to resulting from pregnancy and jaundice. In this connection, it is important to note that all these therapeutic agents are potentially hepatotoxic ⁴⁸. There is an extensive literature covering the hepatotoxic properties of gold salts, salicylates, cinchophen, aminopyrine, bismuth compounds, fever therapy, and hypervitaminosis with vitamin D. This literature will be reviewed in an article to be published ⁴⁹. Transient remissions in arthritis, which I as well as others have observed following surgical operations, may be due to the hepatotoxic properties of the anesthetic employed. Ethyl chloride and solution of tribromoethanol (Avertin[®]) are definitely hepatotoxic,^{48a} and of course chloroform is a hepatic poison (Salter ³⁷). The hepatotoxic effects of the newer barbiturate anesthetics are also being investigated ⁵⁰.

In view of these considerations, one is tempted to speculate as to whether the antiarthritic factor and the potent common denominator of not only pregnancy and jaundice, but also of gold salts, bismuth compounds, fever therapy, cinchophen, and possibly even the salicylates

46 (a) Popper, J, and Steigmann, F. Differential Diagnosis Between Medical and Surgical Jaundice by Laboratory Tests, *Ann Int Med* **29** 469 (Sept) 1948. (b) Lichtman,⁴⁰ p 158.

47 Cantarow and Trumper,²⁷ pp 460 and 448.

48 (a) Ottenberg, R, and Spiegel, R. The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents, *Medicine* **22** 27 (Feb) 1943. (b) Lichtman,⁴⁰ pp 109, 117, 394, 720 and 731.

49 Archer, B. H. The Correlation of Anti-Rheumatic Drugs and Other Therapeutic Agents with Liver Damage, to be published.

50 Pohle, F. J. Anesthesia and Hepatic Function, *Wisconsin M J* **47** 449 (May) 1948.

and aminopyrine, are hepatic damage and/or dysfunction. The hypothesis is made all the more attractive because of the observation made by many students of the subject, that the arthritic patients in whom toxic reactions develop respond best to treatment.³

A case is reported in some detail, as it illustrates the approach to the problem which the author has been using in an attempt to prove the hypothesis that the potent common denominator of remissions in nonspecific arthritis is hepatic damage.

REPORT OF CASE

Past History—O. M., an unmarried Negro woman of 22, was admitted to the Bronx Hospital on July 15, 1948. She was suffering with joint pains of one year's duration. She had been in good health until August 1947, at which time she had polyarthritis, involving the knees, shoulders, elbows, wrists, ankles and finger joints. The condition lasted for four months. At the onset, she was hospitalized for two and a half months at Bellevue Hospital. Roentgenograms of the joints, taken at Bellevue Hospital, revealed the presence of atrophic arthritic changes of the interphalangeal joints, of both knees, and of both elbows. A roentgenogram of the chest showed the presence of diffuse interstitial changes throughout both lungs. The hilar lymph nodes were enlarged, as were the paramediastinal lymph nodes on the right side. A series of electrocardiographs were essentially within normal limits. The result of a Mazzini test was negative. The sedimentation rate was 35 mm in one hour. After the patient's discharge from Bellevue Hospital, subcutaneous nodules developed in the neck, around the elbows, in the hands and over both knees. The arthritis had gradually become worse, and during the three months previous to her admission to Bronx Hospital she had had pain and swelling of the ankles, knees, wrists, fingers and elbows. Since November 1937 she had had a profuse, yellowish-white vaginal discharge.

Physical Examination—Physical examination revealed a chronically ill young Negro woman. The temperature was 99.2 F, the pulse rate 102, and the respiratory rate, 20, the blood pressure was 114 systolic and 78 diastolic. The eyes showed some puffiness of the upper lids, but the pupils were normal. The tonsils were not enlarged, and the thyroid was not palpable, the neck showed a few posterior cervical lymph nodes, which were discrete and tender. The lungs were normal on percussion and auscultation, cardiac examination gave essentially negative results, and the liver and spleen were not palpable. There was tenderness of a diffuse nature over both lower quadrants, and there was some mild tenderness in the hypogastrium. Extension and flexion of the elbows were limited because of pain, but there was no swelling or deformity. The wrists, also, were tender but not swollen. There was swelling of the metacarpophalangeal joints of both hands, and there was fusiform swelling of the finger joints. The epitrochlear lymph nodes were enlarged, and the axillary lymph nodes were also palpable. There was no definite enlargement of the inguinal lymph nodes. Results of the neurologic examination were completely negative.

Laboratory Examination—The blood count showed 3,210,000 red blood cells, hemoglobin concentration of 62 per cent and 7,600 white blood cells, with 61 per cent polymorphonuclear leukocytes and 39 per cent lymphocytes. The Wassermann and Kahn reactions were negative. The sedimentation rate (Win-

trobe method) was 38 mm in one hour. Blood chemistry values were nonprotein nitrogen, 20.8 mg per hundred cubic centimeters, sugar, 88 mg, alkaline phosphatase, 132 mg, calcium, 12.5 mg, phosphorus, 5.4 mg, and serum protein, 8.2 Gm (albumin, 3.6 Gm, globulin, 4.6 Gm). Urinalysis revealed a specific gravity of 1.008, a trace of albumin, innumerable white blood cells, with clumping, and no red blood cells. Urethral and cervical cultures were negative for gonococci. The vaginal smear was normal. Results of an agglutination test for *Brucella abortus* were negative. Repeated aspirations of gastric material revealed no tubercle bacilli, the reaction to the cephalin flocculation test was 1 plus in twenty-four hours and 2 plus in forty-eight hours. The value for the thymol turbidity test was 1.7 units, the sulfobromophthalein test showed 2 per cent dye retention in forty minutes and none in one hour.

Four serial electrocardiograms failed to show any evidence of myocardial damage, the P-R interval was within normal limits.

Roentgenographic Examination—Roentgenograms of the chest showed a diffuse and almost milary type of increased bronchovascular markings and enlargement of the mediastinal and hilar lymph nodes. Similar roentgenograms, made during the patient's three month stay in the hospital, indicated no obvious change. Roentgenograms of the hands showed nothing significant. Roentgenographic examination of the pelvis, shoulders, knees and ankles showed no bony abnormality.

Course—The patient was given a first injection of gold salts on Aug. 4, 1948. The dose was 10 mg of gold sodium thiosulphate, given intramuscularly. Next day, the liver function tests were repeated, and the reaction to the cephalin flocculation test was 1 plus in twenty-four hours and 2 plus in forty-eight hours. The value for the thymol turbidity test was 1.7 units. The sulfobromophthalein test showed 2 per cent retention in forty minutes and none at the end of one hour. A dose of 25 mg of gold salts was given on August 10. After this procedure, the reaction to the cephalin flocculation test was 1 plus in twenty-four hours and 1 plus in forty-eight hours. The value for the thymol turbidity test was 0.7 units. The third dose of gold salts was 35 mg and was given on August 15, the reaction to the cephalin flocculation test remained 1 plus in twenty-four hours and 1 plus in forty-eight hours, but the value for the thymol turbidity test rose to 6.6 units. The value for total serum protein was 8.9 Gm (albumin, 4.5 Gm, globulin, 4.4 Gm), the sulfobromophthalein test showed 5 per cent dye retention in one-half hour and 2 per cent at the end of one hour.

Up to that point, there had been no change in the arthritic condition. On August 25, because of the presence of both arthritis and possible sarcoidosis, the patient was given viosterol (50,000 units twice daily). The dosage was increased on August 27 to 50,000 units three times daily, and on August 31 to 50,000 units four times daily.⁵¹ On August 27, the patient was given 50 mg of gold sodium thiosulphate. On August 28, the level of serum protein was 8.2 Gm per hundred cubic centimeters (albumin, 3.6 Gm, globulin, 4.6 Gm). The reaction to the cephalin flocculation test was 2 plus in twenty-four hours and 3 plus in forty-eight hours. The value for the thymol turbidity test was 8.3 units. The tests were repeated on September 3. The value for serum protein was 7.9 Gm (albumin, 3.4 Gm, globulin, 4.5 Gm). The reaction to the cephalin flocculation test was 2

51 Macrae, D. E. Calciferol for Lupus and Other Conditions, *Brit J Dermat* 60: 159 (May) 1948.

plus in twenty-four hours and 3 plus in forty-eight hours, the value for the thymol turbidity test was 8.1 units. At that time, the arthritis began to show considerable improvement. There was considerably less pain and stiffness of the joints. Objectively, there was a diminution of the swelling of both the knuckles and the fingers, and the patient showed increased motion of both fingers and elbows. All therapy was discontinued at this time because of the definite evidence of hepatic damage.

It is of interest to note that the patient showed evidence of renal irritation at the same time that the liver function tests disclosed evidence of hepatic damage. On August 30, urinalysis revealed a specific gravity of 1.010, a trace of albumin and many red and white blood cells. On September 8, the value for blood uric acid was 5 mg, and the urea clearance was 46 per cent (normal is 75 to 130 per cent). The value for blood urea was 116 mg, and a Fishberg concentration test showed a fixed specific gravity of 1.006.

On September 8, the patient began to complain of tenderness in the right upper abdominal quadrant, accompanied with nausea and vomiting. There was no pronounced rise in temperature. There was no icterus. The sedimentation rate was 38 mm in one hour. The blood count showed hemoglobin, concentration, 59 per cent, 2,780,000 red blood cells per cubic centimeter, 4,000 white blood cells, with 82 per cent polymorphonuclear leukocytes and 18 per cent lymphocytes, alkaline phosphatase, 5.3 mg, total protein, 8.4 Gm (albumin, 4.1 Gm, globulin, 4.3 Gm), icterus index 2, nonprotein nitrogen, 22.4 mg, uric acid, 5 mg, and calcium, 10.8 mg. The reaction to the cephalin flocculation test was 1 plus in twenty-four hours and 2 plus in forty-eight hours. The value for the thymol turbidity test was 8.1 units. The icterus index on repetition was 3. At that time, the arthritic condition continued to improve, and the patient was practically free of pain. She was given a transfusion.

On September 20, the patient still complained of epigastric pain, but the arthritis seemed to be quiescent. The liver function tests were repeated. Blood chemistry values were total protein, 8.5 Gm (albumin, 3.9 Gm, globulin 4.6 Gm), the icterus index, 2, cholesterol, 160 mg, and cholesterol esters, 62 per cent. The reaction to the cephalin flocculation test was 2 plus in twenty-four hours and 2 plus in forty-eight hours, the value for the thymol turbidity test was 8.4 units.

On September 26, nausea was still present. The liver was then definitely palpable and tender. Biopsy of a section of the liver was done, but the section showed no intact parenchyma. Histopathologic examination of the enlarged right epitrochlear lymph node showed disintegration of the lymph follicles, the capsule was for the most part intact, no specific diagnostic features were present.

After October 1, clinical improvement of the hepatitis began. The liver was no longer distinctly palpable, and there was no tenderness in the right upper quadrant. From that point on, there was gradual but definite clinical improvement. The last liver function tests were made on October 12, with these results: Reaction to the cephalin flocculation test was 1 plus in twenty-four hours and 1 plus in forty-eight hours, the value for the thymol turbidity test rose still further, to 9.2 units, the hemoglobin concentration was 64 per cent, there were 3,400,000 red blood cells and 5,950 white blood cells, with 57 per cent polymorphonuclear leukocytes and 43 per cent lymphocytes. On October 23, the patient showed no clinical evidence of hepatitis. There seemed to be a complete remission of the arthritis, and she was discharged from the hospital.

COMMENT

Several points are of interest in this case

1 The patient apparently had two conditions. She had an acute exacerbation of chronic rheumatoid arthritis. In addition, she probably had sarcoidosis, in spite of the negative results of biopsy of the lymph node.

2 Results of the liver function tests made prior to therapy were normal. After administration of two potentially hepatotoxic drugs, gold salts and viosterol in massive doses, a toxic hepatitis suddenly developed. The patient may have had latent sarcoidosis of the liver as a contributory factor, but of that there was no proof.

3 The hepatitis was of the nonicteric type, the icterus index being normal on repeated examinations. (Hepatitis without jaundice is now a recognized entity, but it is sometimes overlooked.)

4 The patient had a prompt and definite amelioration of the arthritis, coincidentally with laboratory evidence of hepatic damage and prior to the clinical onset of the hepatitis.

5 The thymol turbidity test proved to be more sensitive in this case as an indicator of hepatic damage than the cephalin flocculation test. This is consistent with the observation of others,⁵² and with my own growing impression,⁴⁰ that the MacLagen test is a more sensitive test of hepatic damage than is the Hanger test. At the Bronx Hospital, we use both tests and the albumin globulin ratio concurrently, as the three most sensitive and practical tests at our disposal for detection of minimal hepatic damage. We agree with Popper and Steigman⁴⁶ that by using all three tests simultaneously, instead of depending wholly on the cephalin flocculation test, the percentage of positive findings in hepatic damage is increased.

6 Renal function tests were employed to determine any possible nephrotoxic effect of the administration of gold salts and viosterol. Evidence of renal damage was disclosed, although clinically there were no definite signs of renal involvement. However, the underlying renal picture was obscured by the presence of a genitourinary infection in this case.

7 The case points up the necessity of making liver function tests serially in cases of arthritis in which gold salt therapy is being given. At the time of this report, rheumatologists are making routine blood counts, platelet counts and examinations of urine in cases in which chrysotherapy is being given, but it is clear that one must also make liver function tests and not wait for the appearance of icterus before discontinuing gold therapy.

52 Popper and Steigmann⁴⁶ Stillerman, H. B. The Thymol Turbidity Test in Various Diseases, *J. Lab. & Clin. Med.* **33** 565 (May) 1948.

In addition to the hospital case reported, I have followed 8 private cases of nonspecific arthritis, making the cephalin flocculation test while the patients were being treated with gold salts, cinchophen, bismuth subsalicylate, pregnant mare serum (antex® and anteron®) and a foreign protein preparation containing thiamine and cysteine (piocystamine®) ⁵³ In all cases, the reaction to the cephalin flocculation test was negative prior to the institution of therapy. In 3 cases, the reaction to the cephalin flocculation test became positive (3 plus) after therapy. In 1 case, clinical evidence of nonicteric hepatitis developed, which was mild and of short duration, the patient received fifteen injections of bismuth subsalicylate and twenty injections of pregnant mare serum before transient hepatitis developed after one week's use of neocinchophen (15 grams [1 Gm] daily). There was a remission of joint symptoms, which lasted three weeks, and then there was a recurrence of the joint pains, principally in the form of a dorsal spondylitis. In another case of severe rheumatoid arthritis, a 3 plus reaction to the cephalin flocculation test was noted after fifteen injections of bismuth salicylate. There was no clinical evidence of any hepatic disturbance. The patient had a complete remission of the arthritic symptoms except for a stiff but painless shoulder, which yielded to treatment with whirlpool baths. She has continued to receive injections of bismuth subsalicylate once monthly for the six months previous to this report and, thus far, is clinically well. The reaction to the last cephalin flocculation test was negative. Another instance occurred in a typical case of osteoarthritis, in which the reaction to the cephalin flocculation test was 3 plus after nine injections of bismuth subsalicylate. The patient had a complete remission of symptoms two months previous to this report and has maintained improvement to the time of writing. She is still receiving an injection of bismuth subsalicylate once every three weeks. It is of interest to note that the result of the cephalin flocculation test rose to 3 plus when the patient was given 4 grams of thyroid U S P daily, in addition to the injection of bismuth subsalicylate, and of further interest that in the other 5 cases, in which thus far there has been no change in reactions to the cephalin flocculation test, there has been no clinical improvement.

It is emphasized that the latter observations are of a preliminary nature. They are presented at the present time primarily to stimulate the interest of other investigators to join me in a concerted effort to determine whether or not hepatic damage and/or dysfunction is the potent common denominator of remissions in nonspecific arthritis. It is clear to me that there are too many ramifications of this problem

53 Prepared by Lakeside Laboratories

for one investigator, and that the cooperation of many persons will be needed to perform the task. My purpose in the present contribution has been chiefly to suggest a working hypothesis and to point out some methods of study which may help to prove or disprove its validity.

SUMMARY AND CONCLUSIONS

1 There appears to be a basis for the concept that the potent common denominator for the remissions seen in cases of nonspecific arthritis in which the patients become pregnant, or in which jaundice develops, is hepatic damage and/or dysfunction.

2 The same hypothesis may explain the remissions observed in cases of arthritis after the use of gold salts, bismuth compounds, cinchophen, fever therapy, viosterol in massive doses and other hepatotoxic drugs and therapeutic agents.

3 There are six biochemical factors present in pregnancy which operate also in hepatocellular and extrahepatic obstructive jaundice. For the most part, these biochemical changes are the result of hepatic damage and/or dysfunction.

4 These common biochemical denominators, singly or in combination, may possess antirheumatic properties.

5 A method of approach is described which may help to establish the validity of the hypothesis which has been proposed. It consists of the simultaneous administration of gold salts and large doses of viosterol, to produce mild toxic hepatitis. The administration of these agents is carefully controlled by serial liver function tests and renal function tests.

6 As a corollary, this approach suggests a method of treatment of nonspecific arthritis with a new rationale.

The present communication is in the nature of a preliminary report. Its chief purpose is to stimulate the interest of other students in the subject. It is felt that the magnitude and ramifications of the problem are such that they require the cooperation of many investigators.

1964 Grand Concourse

BARBITURATE POISONING

Report of Three Cases

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INCIDENCE

THE POPULARITY of the barbiturates with the medical profession and the laity has contributed greatly to the pronounced rise in the rate of poisonings and deaths due to their use. In 1946 the city hospitals of New York were reporting 1 death every thirty-six hours due to this type of drug.¹

Of the many barbituric acid derivatives which have been made and introduced to the medical profession, about twenty are used in clinical medicine today. Estimates have indicated that 230,000 pounds of barbiturates were manufactured in 1936, whereas 550,000 pounds, or more than twice as much, were produced in 1945.¹ This alone is indicative of the tremendous increase in the use of these drugs.

As each new drug is developed and detailed to the medical profession, it tends to enjoy a period of popularity. In 1936, the fashionable drug to use was phenobarbital or pentobarbital sodium, in 1944, it was seconal sodium® (sodium 5-allyl-5-[1-methyl-butyl] barbiturate), and now it is the latter combined with an equal proportion of amytal sodium® (amobarbital sodium [sodium isoamylethylbarbiturate]), the combination being known as tunal®.

Hambourger made a detailed study of the use of barbiturates in the years 1928 to 1937.² In twelve hospitals in our major cities, with a total admission of 1,254,464 patients, 643 barbiturate poisonings were

From Montefiore Hospital

Read at the meeting of the Pittsburgh Anesthesiology Society, March, 1948

1 Goldstein, S. W. Barbiturates: Blessing and Menace, *J. Am. Pharm. A. (Scient. Ed.)* **36** 5-14 (Jan.) 1947

2 Hambourger, W. E. The Promiscuous Use of Barbiturates: Analysis of Hospital Data, *J. A. M. A.* **114** 2015-2019 (May 18) 1940

recorded, of which 47, or 7.3 per cent, were fatal. In a similar survey made in the same hospitals but covering only a five year period, namely 1940 to 1945, the hospitals were noted as having a total admission of 1,060,275 patients, and 566 barbiturate poisonings were reported¹, in this instance the death rate was not reported. It is noteworthy that in the ten year period 643 cases were reported and that in the latter period, encompassing only five years, 566 cases were reported, however, the total number of admissions was not significantly different. A compilation of records by state authorities in 1936 showed that 355 deaths were due to barbiturates whereas in 1944 there were 502 deaths from this cause. Several states which have shown an increase in deaths due to barbiturates are listed in the accompanying table. The number of deaths is a certain indication of the increasing incidence of barbiturate poisoning.

*Suicidal and Accidental Deaths Caused by Barbiturates**

State	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945
California †	21	31	29	32	56	63	52	93	105	101
Illinois	33	63	56	51	70	70	24	30	33	60
Massachusetts	22	20	20	22	24	35	26	28	22	42
New York †	51	49	62	58	60	66	73	87	98	42
Ohio	28	21	45	32	55	71	42	38	58	72
Oregon †	5	6	5	4	2	6	5	1	4	10
Pennsylvania †	12	15	10	15	18	20	18	21	18	10
Kansas	3	4	3	9	11	3	3	3	1	9
Utah ‡	2	6	5	3	1	1	1	3	2	9
Iowa	4	9	15	9	8	14	5	5	8	9

* Data from National Office of Vital Statistics and State Statistics, United States Public Health Service.

† Indicates states that enacted laws as of Oct. 1, 1945 regulating sale of barbiturates.

‡ Indicates states exercising control of sale of barbiturates by regulation as of Oct. 1, 1945.

SIGNS AND SYMPTOMS

The clinical picture of the deeply narcotized patient is strikingly characteristic. The patient is in coma. His respiration is usually slow and shallow, and cyanosis is present. However, if the patient has acquired pneumonia because of being in a coma for a number of hours he may exhibit rapid, shallow respiration (case 1). The pulse is rapid and the blood pressure very low. If the patient has hypertension the blood pressure may fall into the normal range. The pupils may be centrally fixed and moderately dilated or pinpoint in size, the light reflex may be sluggish or absent. The deep reflexes are absent or depressed, and the Babinski reflex may be positive. Little response is noted on painful stimulation over the supraorbital and mastoid areas. The passage of a stomach tube usually does not elicit a gag reflex. It is wise to examine the skin carefully for bullous and crusted lesions and for areas of pressure necrosis.

The less depressed patient shows no drop in blood pressure, no cyanosis and fairly responsive reflexes. A good sign for the depth of depression is the absence of the gag reflex when a stomach tube is passed. The patient may merely exhibit drowsiness, slightly dilated pupils and a sluggish response to painful stimuli.

DIAGNOSIS

The diagnosis of this condition may present a perplexing problem. An effort should always be made to obtain a history, if the patient is comatose, careful questioning of the relatives and friends should be carried out. A search of the patient's room and clothes should be made. If necessary the police or other authorities should be called in for help. Capsules or boxes with a prescription number may then be found and the physician or druggist may be called in an effort to determine the nature and amount of the drug supplied. This procedure is essential in order to differentiate drug poisoning from other causes of coma. Usually the patient is an intelligent person who has had easy access to the drug used and has been in contact with some phase of medical work. A complete physical examination, blood count, urinalysis, studies of blood chemistry and lumbar puncture when indicated should be done as quickly as possible. This may aid in differentiating uremia, diabetic coma, insulin shock, alcoholism, cerebral hemorrhage and the meningitides. Samples of any medicament that the patient may possibly have taken should be investigated, and it is wise to have the gastric washings and urine analyzed for barbiturates.

The patient should be admitted to the emergency room rather than to a private room or a ward. The emergency room should be equipped with all the necessary materials for immediate treatment so that one is not kept waiting for the suction machine, stomach tubes, oxygen and emergency drugs. Valuable time can thus be saved.

TREATMENT

It is essential to evolve a routine method of treating the patient with barbiturate poisoning. First, adequate oxygenation of the patient is insured by insertion of an oral or nasopharyngeal airway and administration of oxygen by mask or catheter. Should the respiration be so depressed that the patient is breathing only four to eight times a minute, it may be necessary to use some means of artificial respiration to increase the respiratory rate to eighteen or twenty times per minute. It may even be necessary to pass an endotracheal catheter. It is important that the expiratory phase of respiration be just as free from obstruction as the inspiratory phase, for in a person who is depressed and

who tries to exhale against obstruction pulmonary edema may develop in the course of a few hours. Oxygenation of the patient must be instituted before any analeptic drugs are used, for in the presence of severe hypoxia stimulating drugs may be depressant rather than stimulating.³

With the reestablishment of adequate oxygenation, one next turns to the circulatory system. Evidence of depressed circulation is not uncommon. If efforts at resuscitating the patient are to be successful, immediate improvement of the circulation must be brought about. This is done by the immediate establishment of continuous intravenous injection of fluids. If there is no response in the pulse and blood pressure after the patient has received 150 to 200 cc of fluid intravenously it may be necessary to resort to the use of a continuous infusion of 5 mg of phenylephrine hydrochloride (neo-synephrine hydrochloride®) or 100 mg of ephedrine hydrochloride U S P in 500 cc of plasma or isotonic sodium chloride solution U S P. The rate at which the fluid is injected into the patient is governed by the blood pressure. If the blood pressure shows signs of pronounced elevation the rate is decreased, if the pressure remains low the rate is increased. It cannot be too strongly emphasized that it is only by the maintenance of a good circulation that one can treat the patient further.

Once the respiratory and circulatory systems have been checked and the proper treatment instituted, one may examine the patient in an effort to determine the exact degree of depression. Often a patient may be unconscious on admission after taking a relatively small amount of barbiturate, that is, 10 to 40 mg. Pressure on the mastoid process or on the supraorbital ridge may induce some response in such a comatose patient. The pupils may be pinpoint in size or moderately dilated but react to light rather sluggishly. The patient will come out of the coma within a few hours if untreated.

The next step is to empty the gastrointestinal tract of its contents. Thorough washing of the stomach with the use of a large stomach tube may produce a considerable amount of the unabsorbed drug. This should be sent to the laboratory for barbiturate analysis. After the stomach has been thoroughly washed, it is well to put in 2 to 4 ounces (60 to 120 cc) of a saturated solution of magnesium sulfate U S P. as a cathartic, to produce a rapidly acting diarrhea and sweep the remaining traces of the drug out of the small and large intestine, thus preventing further absorption. The patient should be catheterized, since he may have a distended bladder, the specimen should be analyzed to determine the barbiturate present.

3 Frankenstein, H. Personal communication to the authors.

USE OF ANALEPTIC DRUGS

The use of analeptic drugs depends on the depth of narcosis. The patient who responds favorably to the few simple tests mentioned previously is one who has taken a minimal amount of barbiturate, i. e., 10 to 40 grains (0.65 to 2.59 Gm.) or one who has taken a considerable amount but has been brought to the hospital before the full effect of the drug has become manifest. To ascertain the exact status of the patient, a small test dose of one of the milder analeptic drugs such as pentamethylenetetrazol (metrazol®) or nikethamide may be given. Five to 8 cc of metrazol® given intravenously will produce a strong effect in a patient who is in coma but who has taken only a minimal amount of barbiturate. Within only a minute or two the patient may groan, try to move about or even attempt to sit up. Such a patient requires no further treatment.

The patient who does not respond to this test dose may be considered dangerously depressed and requires further treatment. If the patient shows signs of activity in his reflexes after injection of 20 to 30 cc of metrazol® intravenously, an equal dose should be given intramuscularly. In a relatively short space of time, the patient gradually becomes depressed again. Another intravenous injection should then be given, but only 20 to 25 cc of metrazol® is required before the reflexes become active. This is again followed by an intramuscular injection equal to the intravenous dose. The procedure is repeated until the patient responds to intravenous and intramuscular injection of about 2 cc of the drug, when it is no longer necessary to stimulate the patient.

The last type of patient is the one who demonstrates profound narcosis. Picrotoxin U. S. P. is used in treatment of this condition. It is usually administered through an intravenous tube, at the rate of about 0.5 cc per thirty seconds. The quantity given is that necessary to produce an effect on the central nervous system, the earliest manifestations being twitching of the lips and the muscles of the neck or of the fingers. The moment this reaction is observed the intravenous administration of picrotoxin is discontinued, and the quantity which was being given intravenously is then given intramuscularly. When the patient again demonstrates signs of depression the procedure is repeated. Again, the second dose should be somewhat smaller than the first and the third smaller than the second. The reduction is continued to the point where the patient responds to 2 or 3 cc of picrotoxin, at which time metrazol® is substituted and the procedure described for the moderately depressed patient carried out. When an effect on the central nervous system can be obtained with 3 or 4 cc of metrazol® injected intravenously it is wise to discontinue further medication, to avoid overstimulation of the central nervous system.

Amphetamine (benzedine®) and sodium succinate have not been successful in our hands in treatment of the deeply narcotized patient. However, our experience in the use of these drugs has been limited.

In addition to the specific drugs just named, is essential that other supportive therapy be employed. The intravenous injection of fluids to maintain body hydration, and, if the patient remains in a comatose state for several days, the employment of blood plasma, protein hydrolysates and the antibiotic drugs are essential. As the effect of the barbiturate wears off and the patient reaches a state of consciousness,

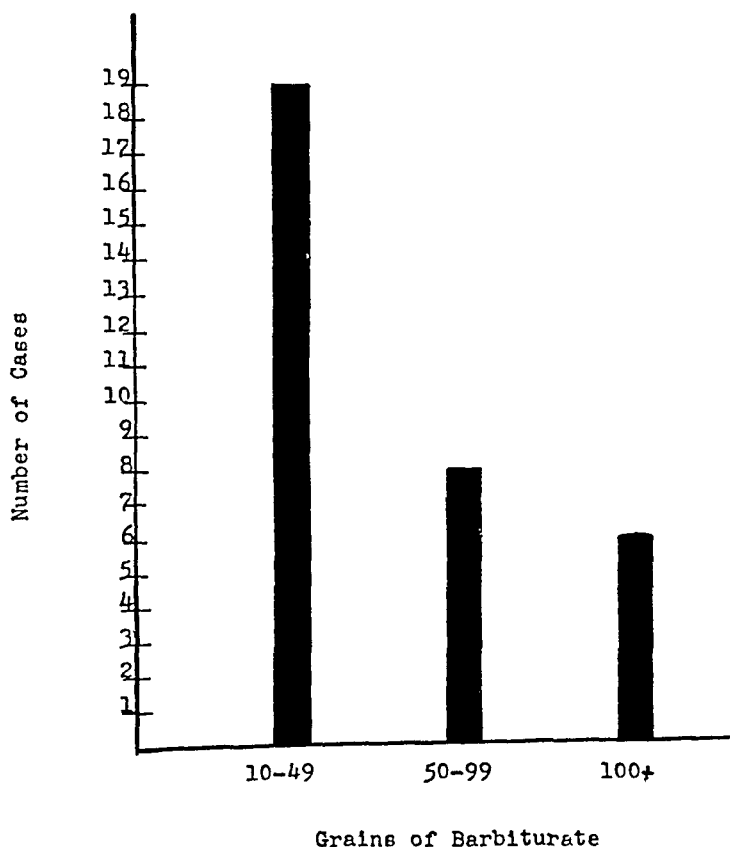


Fig 1—Recorded cases in which a definite amount of barbiturate was known to have been taken

he tends to become extremely restless. It may be necessary to administer 10 to 12 grains (0.65 to 0.78 Gm.) of chloral hydrate U. S. P. or 1 or 2 drachms (4 or 8 cc.) of paraldehyde U. S. P. as a sedative. One cannot overstress the importance of having the patient constantly watched.

The patient almost always should be given antibiotic drugs in therapeutic doses, in order to prevent the almost inevitable hypostatic pneumonia. The patient in deep narcosis usually shows elevation of temperature on admission, probably due to bronchopneumonia but possibly only the hyperthermia produced by the barbiturates.

REPORT OF CASES

Three cases, representing the various depths of narcosis, are presented. They are part of the series of 33 cases summarized in figure 1, in which it will be noted that the majority of the patients took a nonlethal dose of barbiturates.

CASE 1—A white female nurse of 24 was brought to the emergency room in deep coma and obviously cyanotic. She was last known to have been conscious forty-one hours before admission. There were no reflexes. The pupils were moderately dilated and did not react to light. A slight degree of cyanosis was present. The pulse rate was 130 beats per minute, the respiration rate was 60 beats per minute and was shallow. There was no activity of the intercostal muscles, and breathing was mainly diaphragmatic in character. Blood pressure was 100 systolic and 80 diastolic. The medial aspect of both knees showed elongated excavating lesions about 1 inch (2.5 cm) wide, which were raw and weeping. On the right hip, below the iliac crest, an edematous, erythematous patch 3 by 5 inches (7.5 by 12.5 cm) was noted. Bullous lesions of the dorsum of the right foot and hand were also present. The patient was treated with oxygen immediately after the insertion of a nasopharyngeal tube. Intravenous administration of fluids, in the form of dextrose and sodium chloride injection U. S. P., was begun, picrotoxin and metrazol® were given through these. Forty-five milligrams of picrotoxin was given intravenously before a response was obtained, the patient was then given the same dose intramuscularly. Three to 27 mg of picrotoxin was given every hour for a total of 93 mg. Metrazol® was then substituted and given each hour until a total of 68.5 cc had been administered. Only 1 cc of benzedrine® was used. The patient's stomach was washed, and she was catheterized. The intramuscular injection of penicillin was begun. As the blood pressure continued to fall continuous intravenous injection of fluid was begun, with the addition of neo-synephrine hydrochloride®. Since the patient did not respond to the large quantity of analeptic drugs, a spinal puncture was done, but results of the examination were negative. Frequent physical examinations revealed rales in the right lung, and a diagnosis of bronchopneumonia was made. The gastric washings and the urine were negative for barbiturates, but a trace of mercury was found in the urine. In view of these findings, British antilewisite (2, 3-dimercaptopropanol) was given every four hours. On the second day in the hospital, the patient's pupils were less dilated and began to react to light. The urinary output continued to be good, and the intravenous injection of fluids was continued. Suction of the throat produced moaning and coughing. Early in the morning of the patient's third day in the hospital, the blood pressure fell again, administration of 10 mg of neo-synephrine hydrochloride® in dextrose and sodium chloride injection U. S. P. was begun with improvement in the blood pressure. Later on the same day, the patient showed greater response to painful stimulation. Her condition continued to improve, and she then began to complain of sore throat, burning on urination and a cough. She became completely lucid on the fourth day and was discharged from the hospital on the eighth day. On questioning she disclosed that she had taken 90 grains (6 Gm) of seconal sodium®.

CASE 2—The patient, a white male accountant of 35, was brought into the hospital in coma. His wife stated that he had been depressed lately and had been taking seconal sodium® for insomnia. He had had previous association with numerous pharmaceutical companies. A suicide note was found among his belongings, but no evidence of medicaments or bottles was found. Physical examination revealed a well developed and well nourished cyanotic man, in coma, with pinpoint

pupils which did not react to light. All reflexes were depressed. The heart and lungs were normal. There was a laceration of the left wrist. Blood pressure was 110 systolic and 90 diastolic, the pulse rate was 112 and the temperature 99 F. The stomach was washed, and 1 ounce of a solution of magnesium sulfate U S P was injected into the tube. The patient was given 1 unit of plasma, and the injection of 1,000 cc of a 5 per cent solution of dextrose U S P in sodium chloride solution was begun. Five cubic centimeters of picrotoxin, 3 cc of metrazol® and 3 cc of benzedrine® were given. Oxygen was given continuously, and suction was performed frequently after insertion of a nasopharyngeal tube. The patient was catheterized, 28 ounces (794 Gm) of urine was obtained. After the use of analeptic drugs 50,000 units of penicillin was administered every three hours. The patient began to react in a few hours, at which time the temperature was 101 F, it rose the next day to 103 F but fell on the third day to normal. The patient responded in approximately twelve hours. A psychiatrist was consulted, a diagnosis of a reactive depression made and the patient discharged from the hospital in good physical condition. He did not divulge the amount of barbiturate taken.

CASE 3—A white woman of 52 was admitted to the emergency room after having taken 42 grains (272 Gm) of tinal®. She had been depressed because of atrophy resulting from a fracture of the left arm nine months before and was on the verge of a nervous breakdown. She had had six operations on the arm since the fracture. Relatives stated that she had been extremely upset and depressed about the prospects of another operation.

Examination revealed a well developed and well nourished white woman. The blood pressure was 122 systolic and 74 diastolic. The patient's color was good, and she responded to painful stimuli. Reflexes were normal, and the pupils reacted in a normal manner. Numerous factitious lesions were noted over the skin. The stomach was washed, and a nasopharyngeal tube was inserted, but the patient began to moan and groan on its insertion. After 2 cc of nikethamide was given, she sat up and began to talk. She was given penicillin, fluids were injected intravenously, and she was discharged on the fifth day at the hospital.

COMPLICATIONS

The chief complication in barbiturate poisoning is bronchopneumonia. In every case of severe poisoning prophylactic antibiotic therapy should begin as soon as the emergency treatment is completed.

If the patient has been in a state of circulatory collapse there may be inadequate glomerular filtration and poor urinary output, with prerenal azotemia. This condition as well as the pneumonia, which may produce lassitude, stupor, confusion and disorientation, may mislead the physician into believing that the patient is still under the influence of the barbiturates. The condition should be checked constantly with intake and output charts and by determination of the nonprotein nitrogen level of the blood. The use of plasma and of intravenous injections of hypertonic solution of dextrose in sodium chloride solution will help to increase the urinary flow.

Another important and frequent complication is extreme restlessness of the patient after recovery from the acute poisoning. The patient, in coming out of the coma, may rub the skin off his elbows, feet, legs,

knees and back owing to his restlessness. Less pronounced symptoms of anxiety, "nervousness" and irritability are observed as subjective and objective signs. When the patient becomes restless, small doses of chloral hydrate U S P or paraldehyde U S P are effective.

The traumatic effects of insertion of the nasopharyngeal and lavage tubes are also minor problems in convalescence. Hoarseness and "sore throat" are frequent sequelae of the emergency therapy instituted. These conditions usually clear in a day or two. In the meantime, lozenges and gaigles may add to the comfort of the patient.

A natural idiosyncrasy to the drug may manifest itself in the form of myalgic, arthritic or neuralgic pain, which may be severe and may last for days or weeks after the drug has been completely excreted. The



Fig 2—Areas of pressure necrosis along medial aspect of both knees in a case of profound barbiturate poisoning.

pain may appear in paroxysms, it is most frequently localized over the neck, shoulder, scapular region and arms.⁴

An observation made on 2 of our most recent patients revealed peculiar lesions of what appeared to be areas of pressure necrosis along the medial and anterior aspect of the knees (fig 2). One of the patients had deeply excavated lesions along the medial aspect of the knees, with weeping and oozing of serum. The lesions were so severe that skin grafts were necessary before healing took place. Other lesions included crusted areas and bullae on the legs, on the anterior aspect of the knees and on the buttocks.

4 Weiss, S. The Indications and Dangers of Sedatives and Hypnotics with Special References to the Barbituric Acid Derivatives, *Internat Clin* **1** 38-66 (March) 1936.

Other lesions, of a type previously described,⁵ were also observed in these 2 cases. These were bullae which ranged in diameter from 1 cm to 5 or 6 cm and were filled with clear serum, this type of lesion has been described as a nonatopic acquired sensitivity reaction to the drugs. Examination of the skin of each patient may aid in diagnosis, a thorough check of the skin should be made in all cases of coma. Other cases in which pressure necrosis accompanied barbiturate poisoning have come to our attention.

The patient who has an allergy such as asthma, hay fever, angio-neurotic edema or urticaria may exhibit swelling of the eyelids, cheeks or lips.^{5b} With the use of antihistaminic drugs, ephedrine or epinephrine these conditions may be treated successfully.

It has been observed that hyperthermia without the presence of infection is also a frequent complication in barbiturate poisoning. It is difficult to explain this reaction but the effect of the barbiturates on the temperature-regulating mechanism in the brain is thought to be the cause. Pulmonary edema, which in all probability is due to depression of the central nervous system, has also been observed.

Finally, after complete physical recovery, a psychiatrist should be consulted for further treatment of the patient.

SUMMARY AND CONCLUSION

The incidence of barbiturate poisoning, both accidental and suicidal, is definitely increasing. The majority of patients, however, ingest a nonlethal dose.

The patient, when admitted to the hospital, should be treated in the emergency room, where all necessary equipment and drugs should be available. Adequate oxygenation, suctioning, support to the circulatory and respiratory system, elimination of any drugs from the gastrointestinal tract and orientation as to the depth of the narcosis are the most important practical measures in handling such a case. One should not employ the powerful analeptic drugs unless they are definitely indicated. The patient must constantly be watched and nursed. One important measure to prevent pulmonary complications is the use of antibiotic drugs prophylactically.

With the definite increase of poisonings due to barbiturates, there should be stricter regulations regarding dispensation of the drugs. Though many states have laws governing the sale of barbiturates, they are easily obtained by the laity. Further legislative measures are indicated in an effort to reduce the increasing incidence of barbiturate poisonings.

5 (a) Weiss.⁴ (b) Goodman, L., and Gilman, A. *The Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941, p. 145.

AEROSOL AND MICRONIZED EPHEDRINE AND PENICILLIN THERAPY OF DISEASES OF THE LOWER RESPIRATORY TRACT

Treatment of Bronchitis, Bronchiectasis and Intrinsic Asthma

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AND

GEORGE L PACKER, M D

LOS ANGELES

THE SEQUENCE of bronchial infection, bronchiectasis and fibrosis and asthma, with its enormous actual subsequent morbidity, has rightly led to considerable study of the well recognized favorable effects of penicillin inhalation therapy¹ The problem has been one of determining the easiest and least harmful method of placing the penicillin in contact with the offending bacteria Inhalation has circumvented the prime defect of parenteral therapy, namely, deficient circulation of blood in the fibrosed areas, yet there has remained the barrier of the diseased and irritated bronchi and bronchioles

One of us (S J W) had been impressed by observation of the long-continued relief afforded ambulatory persons with diverse types of chronic bronchial asthma by repeated inhalations of mechanically nebulized 3 per cent solution of ephedrine sulfate U S P Similar use of vaporized epinephrine U S P and other bronchodilators was reported several years ago² In the present experimental work, the administration of ephedrine, in either nebulized or dust form, immediately pre-

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1 Levine, E R Inhalation Therapy in Chronic Bronchial Infections, *Dis of Chest* 8:295, 1947 Segal, M S, Levinson, L, and Miller, D Penicillin Inhalation Therapy in Respiratory Infections, *J A M A* 134 762 (June 28) 1947 Prigal, S J Studies with Medicated Aerosols, *Ann Int Med* 28 814, 1948

2 Graeser, J B, and Rowe, A H Inhalation of Epinephrine for Relief of Asthmatic Symptoms, *J Allergy* 6 415, 1935 Richards, E W, Jr, Barach, A L, and Cromwell, H A Use of Vaporized Bronchodilator Solutions in Asthma and Emphysema Continuous Inhalation Method for Severe Asthmatic States, *Am J M Sc* 199 225, 1940

ceded the inhalation of penicillin (nebulized or micronized, respectively) in persons who had previously received diverse forms of therapy. The objects of this study were (a) to observe and compare the effects of ephedrine-penicillin inhalations in the moist and dry forms and (b) to determine an effective and practical form of therapy for ambulatory patients with advanced bacterial bronchitis, with or without attendant bronchiectasis and bronchial asthma.

METHODS

The period of treatment for purposes of this study was empirically set at three weeks. Inhalations were given twice daily (morning and afternoon) for one week and once daily for the next two weeks. Inhalation of 30 mg of ephedrine sulfate U S P over a period of five minutes was immediately followed by inhalation of 100,000 units of crystalline penicillin calcium over a period of ten minutes.³ Oral lavage with plain water followed the treatment.

The vaponefrin® type of nebulizer, attached to the tank of an air compressor unit, proved satisfactory for moist inhalations, the rate of air flow being set at 7 liters per minute. Ephedrine and penicillin dust, ground to an average diameter of 1.5 to 4 microns, was inhaled through the simple oral apparatus described by Taplin and Bryan.⁴ The therapeutic agent was mixed with 5 parts of micronized lactose U S P. Originally, traces of sucrol and vanillin were added for sweetening and flavoring. Sucrol was later eliminated.

PROCEDURE

The series consisted of 39 men, all ambulatory, and with an average age of 53 years. Of these, 31* were in residence in the Domiciliary Home, Veterans Administration Facility, while 7 were treated while undergoing hospitalization because of aggravation of the condition of the respiratory tract and 1 was an outpatient. All had previously been hospitalized and studied at various times, the diagnoses including (a) severe chronic bronchitis, (b) bronchiectasis, (c) emphysema and (d) pulmonary fibrosis. Twenty-seven had varying degrees of asthma. Initially, all patients had a roentgenographic study of the chest, culture of sputum, determination of the twenty-four hour volume of sputum, blood count for eosinophilia, spirometric determination and, when possible, an exercise tolerance step test. Though a roentgenogram of the chest was made before and after treatment of the first 15 patients, little or no change was evident, and a film was made thereafter only before treatment. All patients in the series underwent comparable procedures on completion of the therapy.

Seventeen of the patients received aerosol ephedrine-penicillin solution, while 22 were treated with a micronized ephedrine-penicillin mixture. Two of the former group and 7 of the latter failed to complete the course. Two were found to have pulmonary tuberculosis, 1 had bronchogenic carcinoma, 2 inanition and 3 gave a questionable reaction to treatment.

The bacteriologic analysis consisted in culture on blood agar mediums and bacterial identification of twenty-four hour specimens of sputum, both being made

3 The micronized ephedrine U S P and penicillin used in this study were supplied by George V. Taplin, M.D.

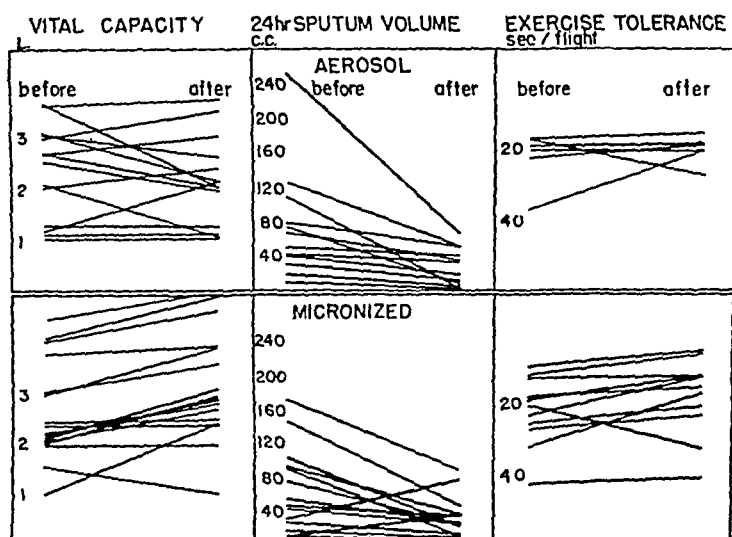
4 Taplin, G. V., and Bryan, F. A. Administration of Micronized Therapeutic Agents by Inhalation or Topical Application, *Science* **105** 502, 1947.

immediately before and after the three week course of treatment. No attempt was made to study the bacterial population, rather, the over-all volume of bacterial changes was determined.

The step test, utilized in the case of persons not incapacitated, provided for ascent and descent of a one flight, ten step staircase to the point of inability to continue by reason of dyspnea. Admittedly, this method gave only an approximate estimate of exercise tolerance because of possible daily individual variation and bronchospasm.

RESULTS

It is apparent from the accompanying chart that both the aerosol and the dust form of ephedrin-penicillin inhalations brought about a considerable reduction in the volume of sputum. Exercise tolerance was increased in both types of therapy, but, while vital capacity was definitely improved with the micronized therapy, results were varied



Comparison of results after treatment with nebulized (aerosol) and micronized (dust) ephedrine sulfate and penicillin calcium

with the aerosol method. Five patients had increased, 5 diminished and 2 unchanged tolerance. No explanation is offered unless it be that the disease was so advanced in several of the latter patients that exercise tolerance tests were not feasible and bronchospasm was easily produced.

Both the moist and the dry therapy resulted in a pronounced reduction in bacterial flora (table 1). Staphylococci, streptococci, diphtheroids and pneumococci were those most commonly eliminated, while other organisms showed a reduction in extent of growth.

Though the 28 patients (14 in each group) who completed the full course were of the same sex and fell into the same general disease classification, a strict comparison is impossible because of variations in constitution and age and in the severity of the disease. The extent to

which infection, emphysema, asthma, bronchiectasis and fibrosis were present were also variables. However, from study of the clinical data (table 2) several impressions of comparative effects may be gained.

No allergic manifestations were observed with the moist therapy, and in only 1 instance was there a complaint of systemic reaction. On

TABLE 1—*Organisms Obtained from Sputum Cultures*

Organism	Patients with Pretherapy Growth			Patients with Post therapy Growth			Patients with No Growth
	Nebulized	Moderate		Heavy	Moderate		
		Ephedrine	and Penicillin		Ephedrine	and Penicillin	
<i>Escherichia coli</i>	1	1			2	1	
<i>Aerobacter aerogenes</i>		2	1	1	1	1	
Diphtheroids	4		2		1		4
<i>Staphylococcus albus</i>	1	2	2			1	4
Hemolytic <i>Staphylococcus aureus</i>	1		2			1	2
Anhemolytic streptococcus	1	1					2
<i>Streptococcus viridans</i>	2	2				2	2
<i>Bacillus subtilis</i>		1	1			3	1
<i>Pneumococcus</i>	1	3				2	2
<i>Hemophilus influenzae</i>	1		2		1	1	1
<i>Neisseria catarrhalis</i>	1	1			2	1	
Hemolytic streptococcus		1	1				2
Totals	13	14	11	1	7	13	20
Micronized Ephedrine-Penicillin Mixture							
<i>H. influenzae</i>			1				1
<i>Str. hemolyticus</i>		2					2
<i>Pneumococcus</i>						1	
<i>N. catarrhalis</i>	1	5	1			7	3
<i>Staphylococcus aureus</i>			2				2
<i>Staphylococcus albus</i>		5					3
<i>A. aerogenes</i>	1	4			1	3	1
<i>Str. viridans</i>		3				2	1
<i>Esch. coli</i>		4			2	3	1
Diphtheroids		1	1			1	1
Beta hemolytic streptococcus	1	1					2
<i>Proteus vulgaris</i>		1				1	
Totals	3	24	5		3	18	16

TABLE 2—*Comparison of Clinical Data for Patients Treated with Aerosol and Micronized Ephedrine and Penicillin*

	Aerosol Form, Number of Patients		Micronized Form, Number of Patients	
	Improved	Unimproved	Improved	Unimproved
Cough	11	3	16	2
Dyspnea	9	5	11	7
Thoracic discomfort and pain	11	3	13	5
Insomnia	7	7	12	6
Anorexia	6	8	9	9

After completion of the course of penicillin therapy, 2 patients treated with the aerosol preparation and 11 patients treated with the micronized preparation required no further epinephrine or ephedrine.

the other hand, 3 persons refused further treatment after several days of dust inhalation, 1 because of nausea following oral dryness and a saccharine taste, a second because of aggravation of urticarial eczema and a third because of headache, insomnia and slight palpebral edema. Several others in this group also complained of oral dryness and a

sweet taste, followed by nausea. These symptoms were slight in degree but lasted about a half hour despite oral lavage on completion of inhalation.

Comparative roentgenograms without the use of iodized oil U S P in the first 15 cases showed change (improvement) in only 1. Undoubtedly, employment of iodized oil U S P in studies of bronchiectasis by the method of Hennell⁵ would have been more fruitful, but this was not feasible. Roentgenograms were taken only at the outset, to rule out carcinoma or tuberculosis.

Tightness in the chest, obviously bronchospasm, was frequently relieved with the preliminary administration of ephedrine. This observation led us to utilize the micronized method of ephedrine inhalation in a one week follow-up study of a number of the asthmatic patients as a substitute for epinephrine by injection. In every instance, relief obtained through inhalation, using 30 mg of ephedrine sulfate, equaled previous relief after hypodermic injection of 0.3 to 0.5 cc of epinephrine solution U S P.

General relief of bronchospasm and pain on coughing during the three week period was approximately equal for the two groups. Similarly, cough was less, with fewer interruptions of sleep, and dyspnea on exertion was less pronounced after treatment. In a number of patients the increased well-being was marked by improvement in appetite.

COMMENT

The subjects of this study, in contrast to a great majority of the patients with infections of the upper respiratory tract briefly treated with dust penicillin by Krasno, Karp and Rhodes,⁶ were victims of chronic infection of the lower respiratory tract, most of them with intrinsic asthma and emphysema. However, there were similarly favorable results in the chronic cases in the two series. The apparatus used in the present work possesses an advantage of simplicity over the face mask used by them, but the more numerous instances of local reaction to inhalation of ephedrine-penicillin dust which we observed were undoubtedly due not to the apparatus but either to the greater pathologic changes in the patients or to the composition of the dust. One local reaction, oral dryness, has been observed with frequent inhalation of nebulized penicillin, as well as of epinephrine,⁷ while the sweet taste was ascribed to the sucrol, since reduction in this con-

⁵ Hennell, H. Reversible Bronchiectasis, *J Mt Sinai Hosp* **14** 1, 1948.

⁶ Krasno, L., Karp, M., and Rhodes, P. S. The Treatment of Asthma by Inhalation of Aerosol of Aminophyllin, *J Allergy* **18** 16, 1947.

⁷ Hartman, M. M. Ethyl-Nor-Epinephrine by Inhalation for Bronchial Asthma. Comparison with Epinephrine, *J Allergy* **17** 106, 1946.

stituent reduced the objection. The nausea appears to be a reflex, it has also been observed with inhalation of aerosols of epinephrine.⁸

The total absence of allergic sensitivity in our patients treated with nebulized ephedrine and penicillin was remarkable, it may have been the result of the preliminary use of ephedrine. The results were almost equally good in the preliminary use of ephedrine dust. The ephedrine was employed primarily as a bronchodilator, but our previous experience in this hospital in the treatment of chronic pulmonary infection with nebulized penicillin alone, after the method of Barach and others,⁹ included secondary cutaneous allergic manifestations similar to those reported by Engelsher.¹⁰ The majority of our cases fall into the same group of "intrinsic or bacterial" asthma as those of Engelsher, yet our therapeutic results were much better, and it is probable that this result also, in a measure, may be ascribed to the preliminary use of ephedrine. Other aerosol bronchodilators, such as suprel,¹¹ (racemic 1-[3-4-dihydroxyphenyl]-2-isopropylaminoethanol) or aminophylline U S P¹² undoubtedly possess advantages over ephedrine, but their general antiallergic properties are not yet sufficiently well defined to stand comparison. Local pulmonary vasoconstriction as a means of retarding systemic absorption of the penicillin, was a reason for the preliminary use of ephedrine.

In a comparison of the practical aspects of the dust and nebulized forms of administration, there can be no question as to the value of a method of which avoids the use of oxygen tank, nebulizer and compressor and the tedium of preparing sterile solutions. That appreciable levels of penicillin in the blood are quickly attained after administration of penicillin dust has been well demonstrated.¹³ We have not determined these levels, local bacterial contact with penicillin is of greater importance in intrinsic asthma. Evidence of the equal efficacy of the dust inhalation and the aerosol method is definite as regards the over-all volume of bacterial change.

The demonstration of the reversibility of bronchiectatic change after penicillin inhalation⁵ gives new hope to persons with chronic infectious pulmonary disease. We have not as yet determined the length of time for which our patients retain improvement without continuance of

8 Koelsche, G. A. *Aerosol Therapy*, J. Allergy **19** 47, 1948

9 Barach and others, cited by Koelsche.⁸

10 Engelsher, D. L. *Aerosol Penicillin*, J. A. M. A. **131** 61 (May 4) 1946

11 Segal, S., and Beakey, J. F. *The Management of Bronchial Asthma* Ann. Allergy **5** 317- 1947

12 Prigal, S. J., Brooks, A. M., and Harris, R. *The Treatment of Asthma by Inhalation of Aerosol of Aminophyllin*, J. Allergy **18** 16, 1947

13 Taplin and Bryan.⁴ Krasno, Karp and Rhodes.⁶

therapy or the frequency and extent to which inhalation therapy by this method is necessary in order to maintain or enhance the improvement. It is necessary to make controlled long term studies on such patients in order to shed light on these matters.

SUMMARY

Comparative therapeutic studies on each of two series of 14 patients with chronic bronchial infection, chiefly with bronchiectasis, emphysema and intrinsic asthma, are summarized as follows:

1 The patients in the series treated for three weeks with nebulized (aerosol) ephedrine sulfate U S P followed by aerosol of penicillin calcium gained considerable benefit, as indicated by reduced volume of sputum, increased exercise tolerance, reduced dyspnea, cough and chest discomfort, improved sleep and appetite and decreased epinephrine requirement.

2 The patients in the series treated for an equal period with micronized (dust) ephedrine sulfate U S P followed by micronized penicillin calcium derived apparently equal benefit in the same details, with an additional increase in vital capacity. Minor reactions, such as oral dryness, saccharine taste and nausea, appeared in this group.

3 Allergic manifestations rarely accompanied the therapy. Inhalation of dust ephedrine will frequently replace the hypodermic administration of epinephrine for asthma.

4 Bacteriologic studies indicated approximately equal effectiveness of moist and dry therapy.

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REFLEX VASODILATATION BY BODY HEATING IN DIAGNOSIS OF PERIPHERAL VASCULAR DISORDERS

A Criticism of Methods

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ALTHOUGH Brown-Séguard,¹ as early as 1858, called attention to the clinical importance of differentiating arterial spasm from arterial occlusion, routine tests to differentiate between the two have been introduced only within the last twenty years, i e, since the study of peripheral vascular diseases has become a recognized specialty in the practice of medicine. Numerous methods have been used at various times (general anesthesia, spinal anesthesia, paravertebral block, peripheral nerve block, injections of typhoid vaccine, injections of sympatholytic drugs, immersion of one or two extremities independently in hot water, and the use of electrically heated sleeves, boots and mattresses), many of which do not lend themselves to routine clinical examination, particularly in the patient's home. Of all the methods mentioned, reflex vasodilatation as produced by body heating is the most practical, the most reliable and the only one not fraught with possible danger to the patient. It is also a method by which vasodilatation may be maintained and repeated ad lib. We ourselves have been using the method for the last fifteen years, in well over 3,000 tests, without ever recording the slightest ill effect. After the critical investigations by Uprus, Gaylor and Carmichael,² in 1936, it appeared that the existence of the humoral mechanism underlying the reaction had been well established. In 1940, however, Duthie and Mackay,³ after apparently well planned experiments, postulated a nervous mechanism. Although the view was in sharp contrast to any theories held before, Duthie and Mackay have not been taken up in their contentions at the time of this

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1 Brown-Séguard, C E. Course of Lectures on the Physiology and Pathology of the Central Nervous System, Philadelphia, Collins, 1860

2 Uprus, V, Gaylor, J B, and Carmichael, E A. Vasodilatation and Vasoconstriction in Response to Warming and Cooling the Body. A Criticism of Methods, *Clin Sc* 2 301, 1936

3 Duthie, J J R, and Mackay, R M I. Vasomotor Reflexes in the Control of Body Temperature in Man, *Brain* 63 295, 1940

report Learmonth,⁴ who reviewed the application of reflex heat in surgical practice, wrote that no finality had been reached as to the mechanism concerned in reflex vasodilatation and, after citing Duthie and Mackay, concluded by saying, "here at the moment the matter rests" On account of the importance of the method in both the diagnosis and the treatment of disturbances of the peripheral circulation, it appeared essential that the mechanism be elucidated and critically examined anew

METHODS AND MATERIALS

The methods used in the present study followed closely those previously described, for details, one should refer to the earlier papers (Goetz⁵) Continuous records of the peripheral circulation were obtained with the Goetz optical digital plethysmograph^{5a} The toe is enclosed within a glass plethysmograph, which is connected to a pipet graduated in hundredths of cubic centimeters, and containing a

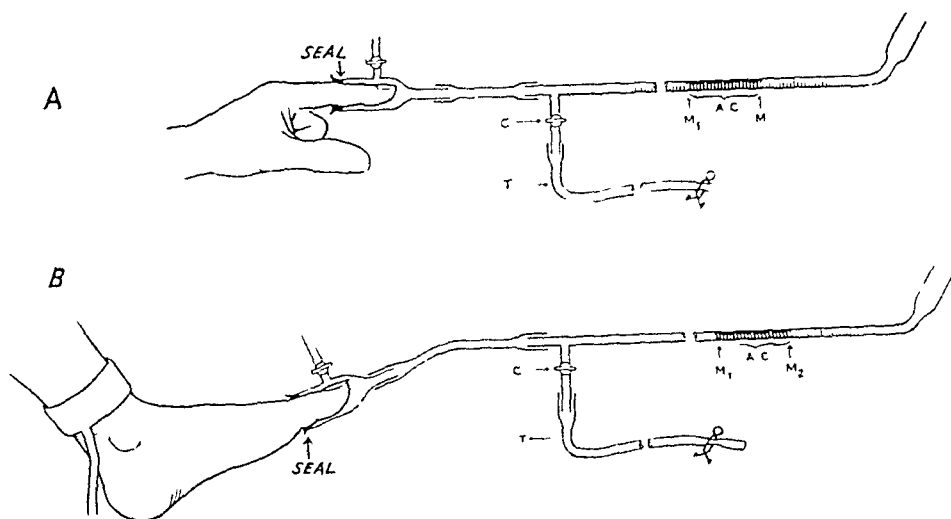


Fig 1—The principle of our optical digital plethysmograph *A*, as applied for a finger, *B*, as applied for a toe *AC*, alcohol column, *C*, tap, *T*, rubber tubing and clamp for adjusting alcohol column in pipet, *M*₁ and *M*₂, menisci of alcohol column, the movements of which are recorded

4 Learmonth, J R Reflex Vasodilatation in Surgery, Edinburgh M J 50 140, 1943

5 Goetz, R H (a) Plethysmography of the Skin in the Investigation of Peripheral Vascular Diseases, Brit J Surg 27 506, 1940, (b) The Rate and Control of the Blood Flow Through the Skin of the Upper Extremities, South African J M Sc 8 65, 1943, (c) The Classification and Diagnosis of Peripheral Vascular Diseases, ibid 19.91, 1945, (d) The Rate and Control of the Blood Flow Through the Skin of the Lower Extremities, Am Heart J 31 146, 1946, (e) Clinical Plethysmography, South African M J 22 391 and 422, 1948, (f) The Effect of Changes in Posture on the Peripheral Circulation with Special Reference to Skin Temperature Readings and the Plethysmogram, Am Heart J, to be published

5a A portable model of our digital plethysmograph is now manufactured and is available from Hilger and Watts Ltd, Scientific Instrument Makers, 98, St Pancras Way, London, NW 1, England

column of alcohol (fig 1) When the plethysmograph is sealed with petrolatum, the volume changes in the toes are transmitted to the alcohol column, the movements of which are enlarged and projected onto the paper of a recording camera Registration is effected by the meniscus of the alcohol column, which casts a shadow on the photographic paper This arrangement makes possible exact and undistorted measurement of changes in skin volume, a difference of 0.001 cc being recorded easily Whatever the enlargement, no calibration is required, since the graduations of the pipet appear as white horizontal lines on the film The sensitive device allows not only direct registration of the pulse volume, but also calculation of the arterial inflow at any one moment by means of the so-called venous congestion test^{5b, d, e} The respiration was continuously recorded simultaneously with the taking of the plethysmogram in some of the tests, and the skin temperature of one or more digits was measured by means of a mirror galvanometer and a thermocouple

All observations were conducted in a draught-free and noiseless room The room temperature was kept constant during the experiments, but no effort was made to control the relative humidity Elsewhere,^{5f} it will be shown that posture plays an important role in the response of both the skin temperature and the circulation to body heating Therefore, all tests were carried out with the patient resting comfortably on the couch illustrated in fig 2A, like the tank used for body heating, it was devised in our laboratories some years ago for the routine investigation of the peripheral circulation The tank used for immersion of the limbs was fitted with an immersion heater and a stirring device, and the water temperature was thermostatically controlled (fig 2B) In order to obtain reflex vasodilatation of the upper extremities, both lower limbs were immersed in the tank to a point 6 inches (15 cm) above the ankle To obtain dilatation in the lower extremities, one arm was immersed to a point 6 inches (15 cm) above the elbow The water temperature was kept constant at 45°C, and vasodilatation was maintained for thirty minutes, as suggested by Gibbon and Landis⁶ With the exception of the extremity which was being tested, the subject was covered with two woolen blankets, to prevent the dissipation of heat

For occlusion of the peripheral blood flow of the upper extremity, as required in some tests, the ordinary blood pressure cuff was used The cuff was well fixed around the arm For occlusion of the circulation through the lower extremity a special blood pressure cuff had to be made, the rubber bag of which was 18 inches (45 cm) long, so as completely to surround the thigh Special care was taken that the blood pressure in the cuff during the obstruction remained well above the systolic pressure during the course of the experiment The pressure required to occlude the peripheral blood flow was first determined by plethysmographic means

Method of Recording Blood Pressure Objectively (and, When Necessary, Simultaneously in Two Extremities) with the Digital Plethysmograph—The plethysmogram of a digit is recorded and the arterial circulation occluded by a blood pressure cuff, inflated to well above systolic blood pressure With the artery occluded, the plethysmogram naturally does not record any pulse volume, and after certain initial changes in digital volume⁷ have occurred, the plethys-

6 Gibbon, J H, and Landis, E M Vasodilatation in the Lower Extremities in Response to Immersing the Forearm in Warm Water, *J Clin Investigation* **11** 1019, 1932

7 Goetz, R H Der Fingerplethysmograph als Mittel zur Untersuchung der Regulationsmechanismen in peripheren Gefassgebieten, *Arch f d ges Physiol* **235** 271, 1935

mogram presents a straight line (fig 3) The pressure in the cuff, which is recorded simultaneously with the plethysmogram, is then gradually released, and the point at which the pulse first recurs is taken as systolic blood pressure (fig 3) Since our plethysmograph permits registration of the blood flow in two extremities simultaneously, it is possible to record simultaneously the blood pressure in two limbs, e g, a leg and an arm In this procedure, the two cuffs

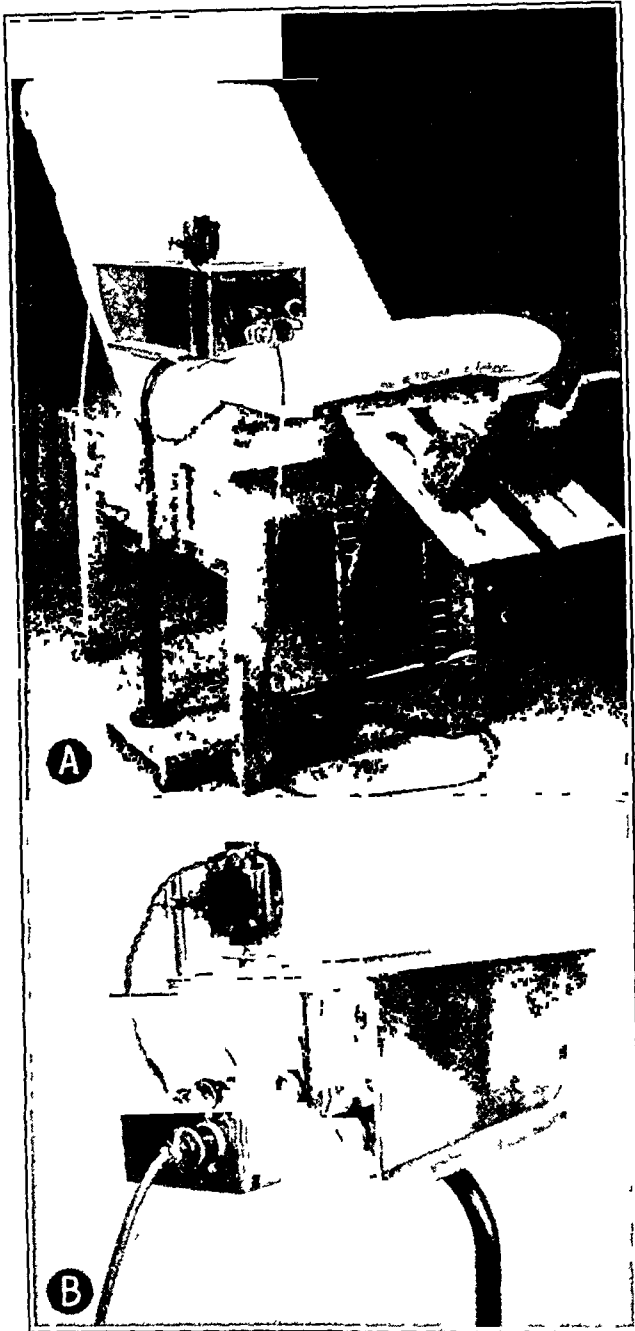


Fig 2—*A*, examination couch, as developed by us for plethysmographic investigations Note the adjustable back and foot rests The bath for body heating is on a movable stand, its height can be adjusted for the arm or the feet The back of the couch can be lowered, so that the couch can be used as a general examination table (Goetz ^{5e}) *B*, arm or foot bath, as devised in our laboratories for producing ablation of central vasoconstrictor tone by body heating The heating is thermostatically controlled and adjustable Note stirring device, and pilot light to indicate whether or not the immersion heater is in operation

are connected via a T piece to the manometer, so that they may be inflated or deflated simultaneously. Any difference in pressures, permitting the return of blood flow, is then easily recorded. As demonstrated in figure 3, in the subject tested a pressure of 160 mm of mercury was required to occlude the vessels of the lower extremities, but 100 mm sufficed for the upper. The method, then, is an objective one of recording apparent differences in blood pressure in the upper and lower extremities.

A pressure of 80 mm above the systolic pressure, determined in this way, was used in order to occlude the peripheral circulation during those experiments in which body heating was carried out on a limb with occluded circulation.

Duthie and Mackay³ observed that heating of the occluded arm caused pain, often of a severe degree. They found that when the arm was cooled before occlusion was applied, immersion in hot water could be tolerated for a consid-

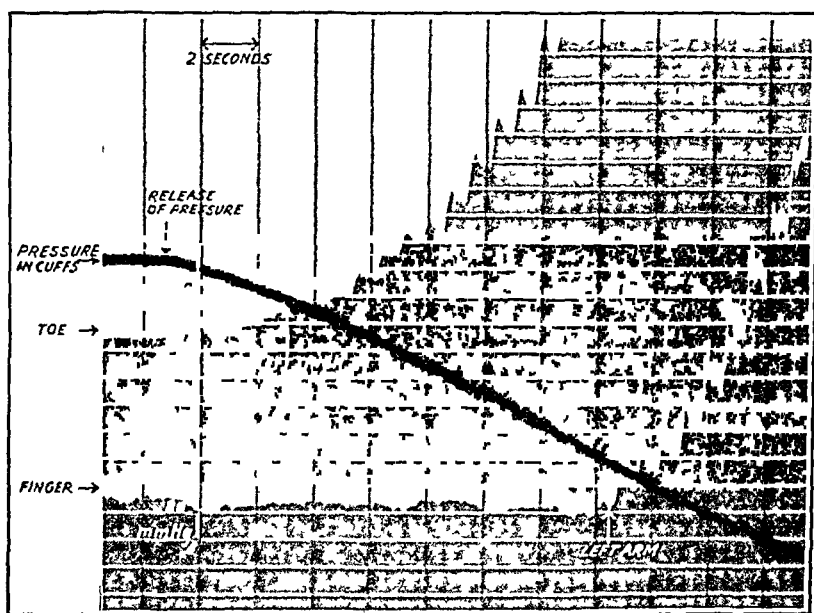


Fig 3—Registration of "blood pressure" simultaneously in the upper and lower extremities by means of plethysmography. Note that the initial pressure of 175 mm occludes blood flow in both the upper and the lower extremity. On release of the pressure within the cuffs, the blood flow resumes in the toe at a pressure of 160 mm and in the finger at a pressure of 100 mm.

erable period with relatively little discomfort. We therefore followed their advice by immersing the extremities in water of 10 C for a period up to ten minutes before occluding the circulation and applying heat to the occluded limb.

RESULTS

Effect of Body Heating on Peripheral Circulation in Normal Subjects—Figure 4 illustrates the typical result obtained in a straightforward routine test, as we carry them out in the Department of Peripheral Vascular Diseases of Groote Schuur Hospital in all cases of proved or suspected vascular disease. In the graph, the response of the pulse volume, the digital volume, the rate of blood flow and the skin tempera-

ture were plotted from the plethysmogram, which was continuously recorded during thirty minutes' body heating

The pulse volume and the digital volume respond first, after four minutes, in this instance, an appreciable rise was recorded in the

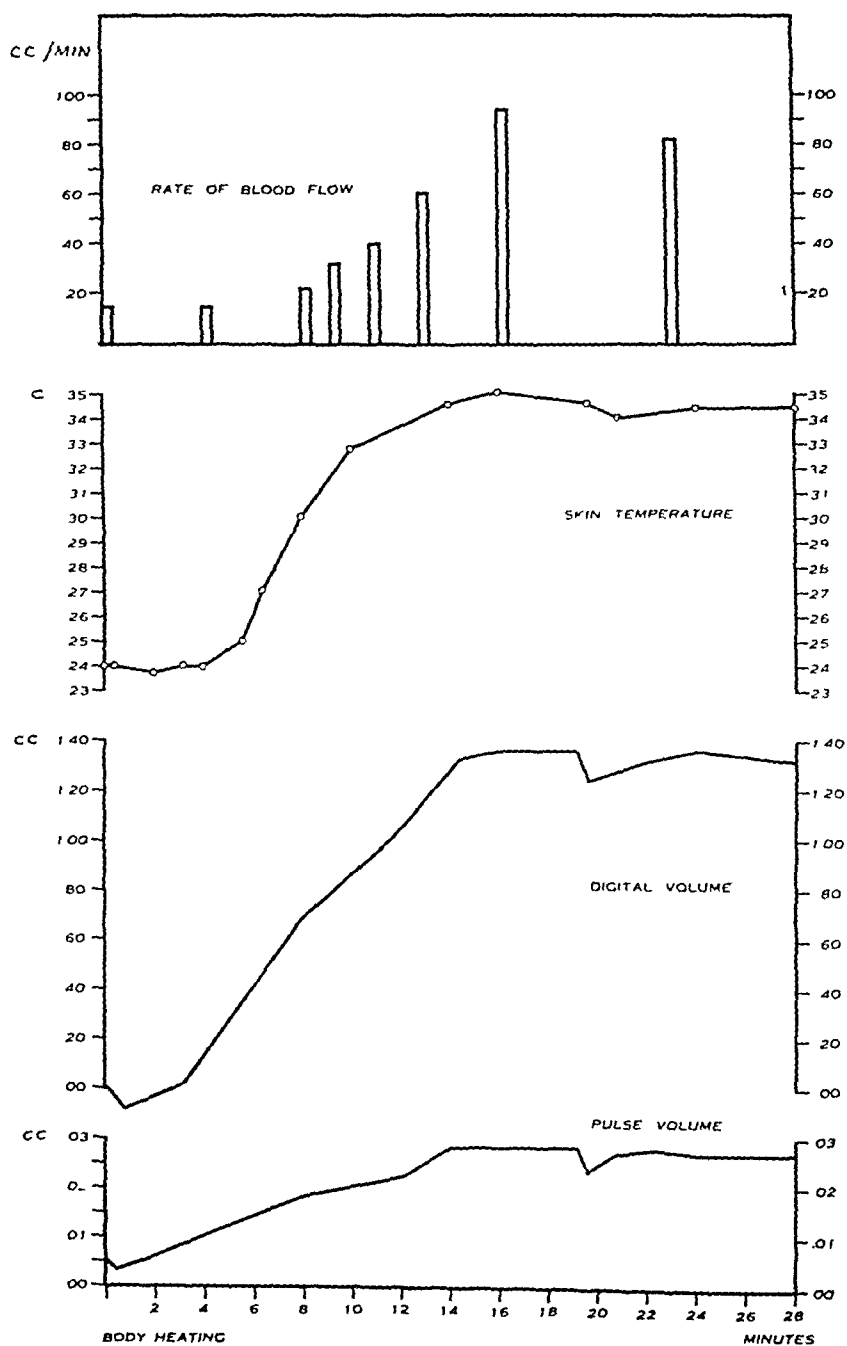


Fig 4—Effect of body heating on blood flow in a normal person (graphs prepared from a plethysmogram) All values were recorded simultaneously and continuously

former (Only after there has been an increase in peripheral blood flow for some time does the skin temperature start rising) In this instance, the pulse volume reached its maximum after fourteen minutes

and the digital volume, after sixteen minutes. In the meantime, the rate of blood flow, as calculated from the venous congestion tests, increased from 16 to 80 cc per minute per hundred cubic centimeters of tissue. The skin temperature, although lagging behind somewhat at the outset, as is usual, also reached its maximum of 32 to 34 C (89.6 to 93.2 F) after sixteen minutes. The relation between the pulse volume and the rate of blood flow, on the one hand, and the skin temperature, on the other, is clear, and it is obvious that the pulse volume, as indicated in the cuttings of the original film (fig 5), furnishes a clear picture of the state of the peripheral circulation at any one moment. Before body heating, with the patient at rest, the pulse volume registered 0.005 cc. After ten minutes' body heating, it had risen to 0.015 cc, and after twenty minutes, 0.025 cc was recorded. The latter figure we refer to as the vasodilatation level. It was found that 0.02 cc was about the lowest value recorded during full dilatation in any normal subject, and it is therefore referred to as the minimum vasodilatation level (Goetz^{5d}). Failure of the pulse volume to reach this minimum vasodilatation level, therefore, has to be accounted for. As a rule, a pulse volume below 0.02 cc during full dilatation indicates organic arterial interference.^{7a}

Effect of Arterial Occlusion of an Immersed Limb on Response of Peripheral Circulation to Body Heating—The results charted in figure 6 contrast with the findings just described. In this instance, skin temperature, digital volume and pulse volume were recorded continuously for a normal subject, whose lower limbs at the outset were fully constricted. However, before body heating was commenced, the blood flow to the lower extremities was occluded. Only thereafter were the lower extremities immersed in water of 45 C. As demonstrated in figure 6, body heating was carried out for twenty-eight minutes, during which time there was no change whatsoever in the pulse volume or the digital volume of the second left finger, or in the skin temperature of the second right and the third left finger. The occluding cuff was then released, body heating was continued and, after three minutes, the pulse volume started rising, followed a few minutes later by the digital volume and the skin temperature. Within twenty-two minutes, all values reached vasodilatation level. The pulse volume was well above 0.02 cc and the skin temperatures, well above 34 C, and the digital volume had risen by 1.60 cc.

7a The pulse volume naturally depends on the amount of tissue enclosed within the plethysmograph, therefore, the pulse volume is different for various subjects during full dilatation. However, comparable indexes of the pulse volume may be obtained easily by correcting the pulse volume to a mean value (conveniently, 15 cc), by means of a simple formula (Goetz^{5d}). A value of 0.02 cc as minimum vasodilatation level therefore refers to the mean digital volume of 15 cc. When the volume of the digit is larger, a correspondingly higher value is normal.

Cuttings of the original film (fig 7) give a clear picture of the failure of body heating to produce peripheral vasodilatation while the peripheral circulation of the immersed limbs was occluded. Figure 7A illustrates the pulse volume before the test, figure 7B was recorded after twenty-seven minutes' body heating, plus occlusion, and figure 7C, twenty minutes after the release of occlusion, while body heating was still being carried on. The pulse volume did not change appreci-

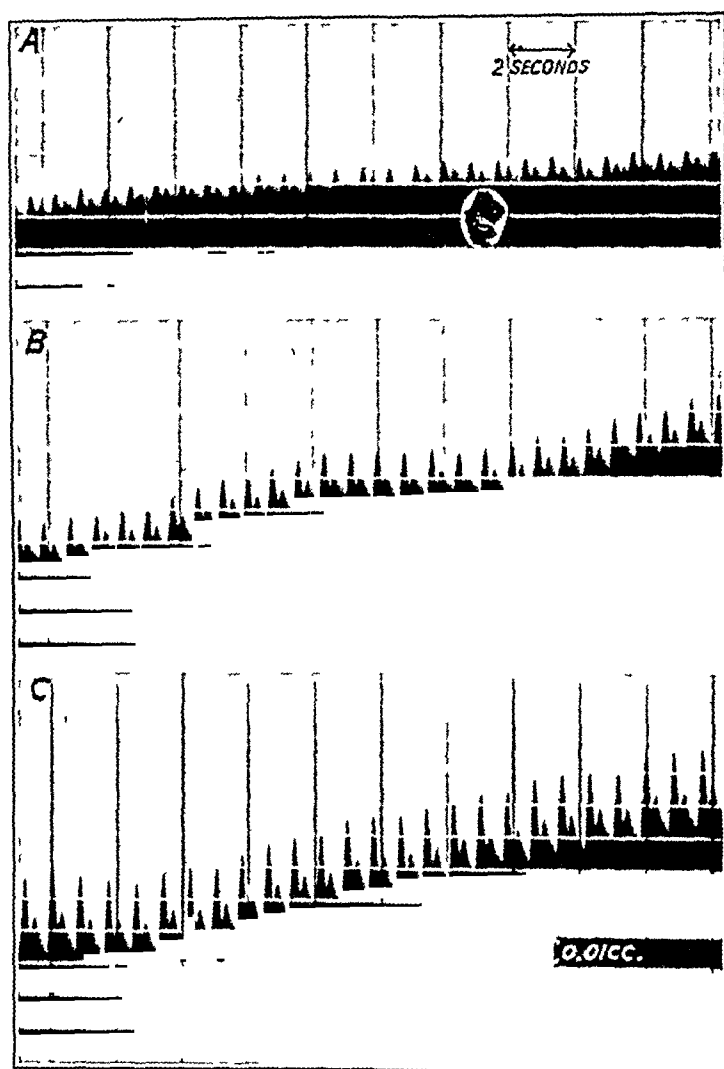


Fig 5—Cuttings from the original plethysmogram used in preparation of figure 4, illustrating the release of vasomotor tone in the first left toe, as obtained by body heating. A, pulse volume before body heating (± 0.005 cc), B, during body heating (± 0.015 cc), C, after thirty minutes' body heating (± 0.025 cc)

ably between the recording of 7A and 7B, but there was complete release of vasomotor tone following twenty minutes' body heating, after the circulation in the immersed limb had been restored (fig 7C)

Exactly the same result was obtained when the blood flow in the lower extremities was recorded and one of the upper limbs immersed (fig 8). There was a slight change in blood flow in the left big toe

during body heating while the peripheral blood flow of the immersed upper limb was occluded, but the change was of no significance, as indicated in figure 9. However, within five minutes of release of occlusion, a sudden and rapid rise in both digital and pulse volume was recorded, followed with a similar response in skin temperature. Within

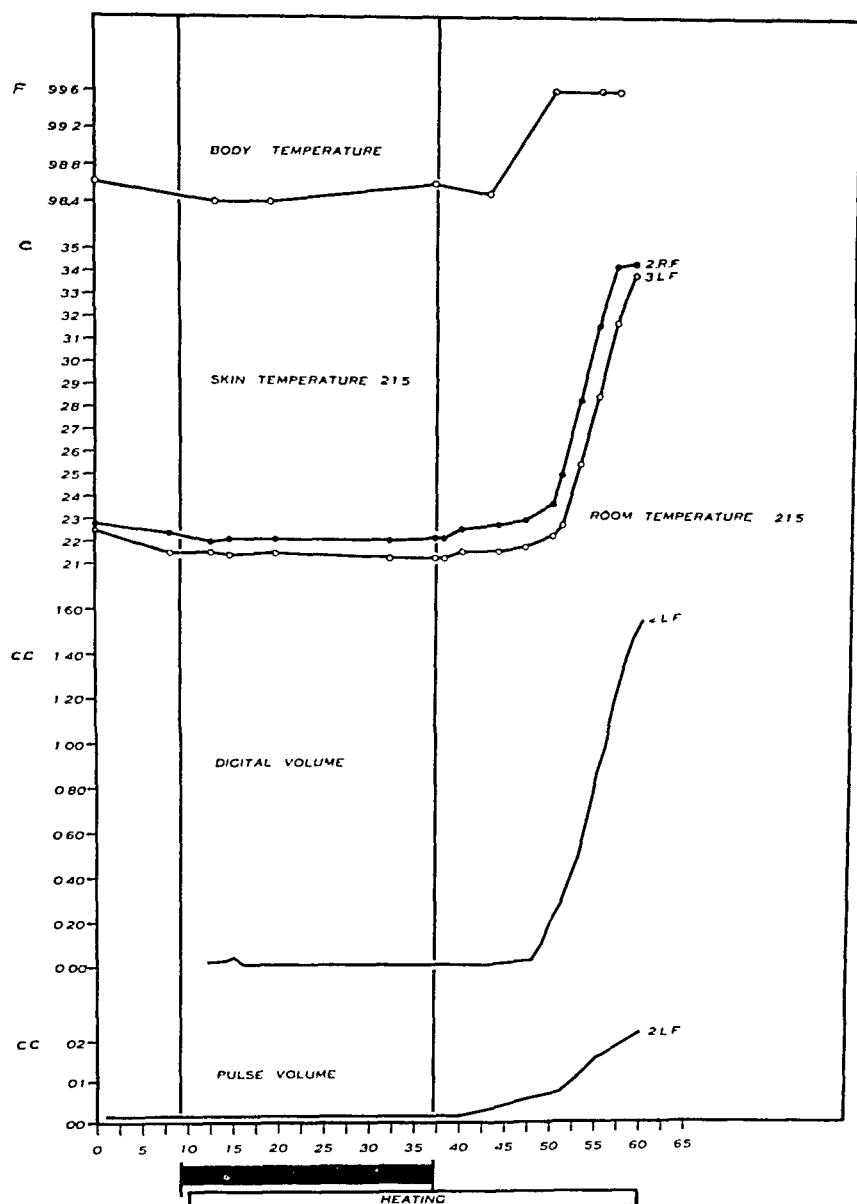


Fig 6—Graph prepared from an original plethysmogram on which were registered continuously the pulse volume and digital volume of the second left finger and the skin temperature of the third left and second right finger. The graph demonstrates the failure to obtain vasodilatation in the upper limbs by immersion of both lower limbs in water of 45 C when the circulation in the latter was occluded first and kept occluded during the period of body heating. Black area indicates period of occluded circulation in lower limbs, white area, period of body heating. Note prompt dilatation on release of occluded circulation in lower (immersed) limbs.

thirteen minutes of the release of occlusion, all values reached full vasodilatation level. Figure 9 shows the cuttings of the original film, illustrating the course taken by the pulse volume. Figure 9A indicates

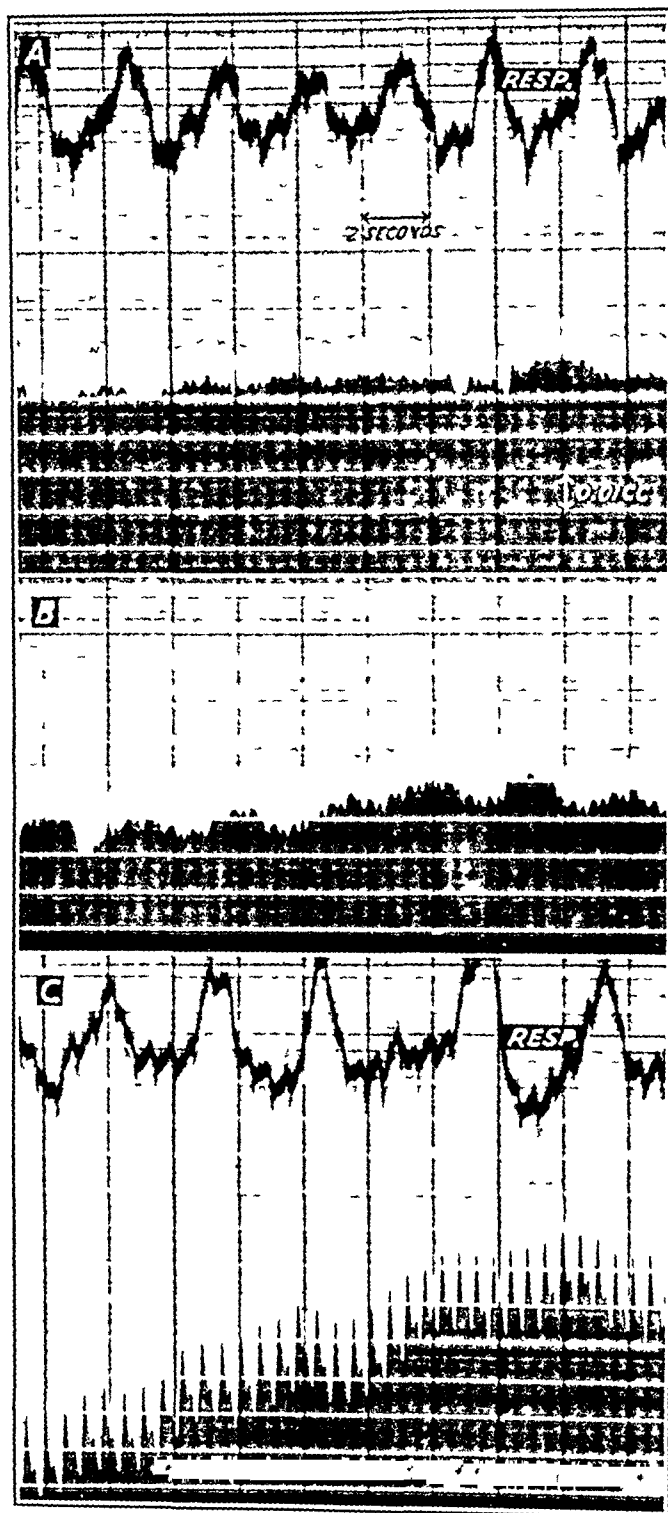


Fig 7—Cuttings from the original plethysmogram referred to in fig 6. Pulse volume (second left finger) *A*, before occlusion and heating, *B*, after twenty-seven minutes' body heating, plus occlusion, *C*, twenty minutes after release of occlusion, but with body heating continued. Note failure to dilate between recording of *A* and *B*, and complete and full vasodilatation in *C*.

the pulse volume just before release of occlusion, i e , after twenty-six minutes' body heating. Nine minutes after occlusion had been released, figure 9B was obtained. The pulse volume had increased from 0.003 cc to 0.007 cc. Three minutes later, the pulse volume reached 0.016 cc, demonstrating the rapidity of dilatation once occlusion was released. Figure 10 shows results of the venous congestion test for the same person. At a point just before occlusion was released and when body

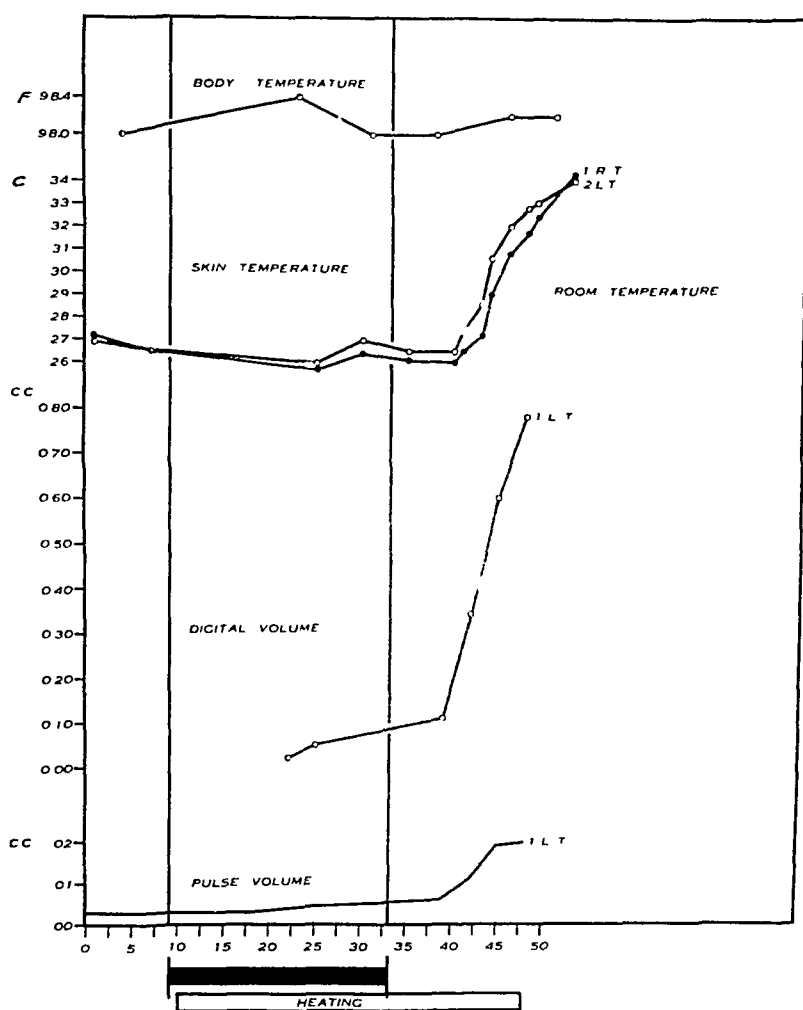


Fig 8—Failure to produce vasodilatation in the lower extremities by immersion of the occluded upper limb. Note prompt vasodilatation after release of the circulation while heating was continued. Black area indicates period of occlusion of circulation of upper extremity, white area, period of body heating.

heating had been carried on for twenty-six minutes, the rate of arterial inflow was 0.008 cc per two seconds (exactly the same as before the test). Nine minutes after occlusion had been released, the arterial inflow had already risen to 0.04 cc per two seconds, and after an additional four minutes' body heating, the arterial inflow had increased to

0.08 cc per two seconds. There was, then, a tenfold increase in the actual rate of blood flow following release of occlusion.

Failure of Occlusion of the Arterial Circulation in an Immersed Limb to Abolish Reflex Dilatation by Body Heating—Although, as a rule, no reflex vasodilatation was obtained on immersion of an occluded limb for thirty minutes into water of 45 C (figures 6 and 8), in two tests there was an increase in the peripheral blood flow, which had to be accounted for. However, the level of full vasodilatation was not reached. Furthermore, in both cases we proved to our satisfaction that occlusion of the arterial circulation could not have been complete, in subsequent tests, with higher occlusion pressures these 2 subjects failed as usual, to show dilatation. It was after these tests that we insisted that the exact pressure assuring occlusion of the peripheral blood flow in the immersed limb be determined plethysmographically beforehand, as shown in figure 3.

In investigating the cause of the failures, it was noted that there might occur a considerable rise in blood pressure as body heating was in

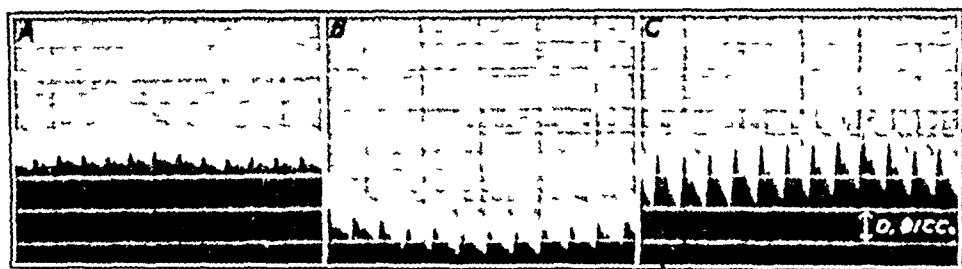


Fig 9—Cuttings from the original film referred to in figure 8. Pulse volume (first left toe). A, just before release of occlusion (note small pulse volume), B, nine minutes after release of occlusion, but with continued body heating, C, eighteen minutes after release of occlusion, but with continued body heating.

progress. The rise occurred only in those tests in which the arterial circulation of the immersed limb had been occluded. Figure 11 illustrates such a test. The effect on the peripheral circulation was the same as before, there being no vasodilatation while the arterial circulation in the immersed feet was occluded. The systolic blood pressure at the commencement of the test was 110 mm in the arm. The pressure required at the thigh to occlude the blood flow in the leg was 170. The blood pressure in the arm rose steadily in the latter half of the test, eventually reaching 140. If one assumes that the pressure in the thigh rose to the same degree, it was about 200 at the end of the test. The reason for the rise in blood pressure is twofold. Firstly, a considerable amount of pain is experienced by the patient in the occluded limb as body heating progresses, and as a rule numbness and complete paralysis of the immersed limb develop, as a result of the pain, the subject becomes extremely apprehensive and uneasy. Both the pain and the fear cause

a considerable rise in blood pressure. An example of how uneasy a subject may become is the experience of a colleague, who had had the procedure fully explained and who volunteered for the investigations. When her hand became paralyzed she begged us to discontinue the test, although it was long before thirty minutes' body heating had been completed. Secondly, Alam and Smirk⁸ demonstrated that metabolites, accumulating in voluntary muscle when the circulation is arrested, raise the blood pressure. "This reflex rise in the blood pressure is not due mainly to the pain produced." In some subjects, the rise in blood pressure is considerably higher than that shown in figure 11. It there-

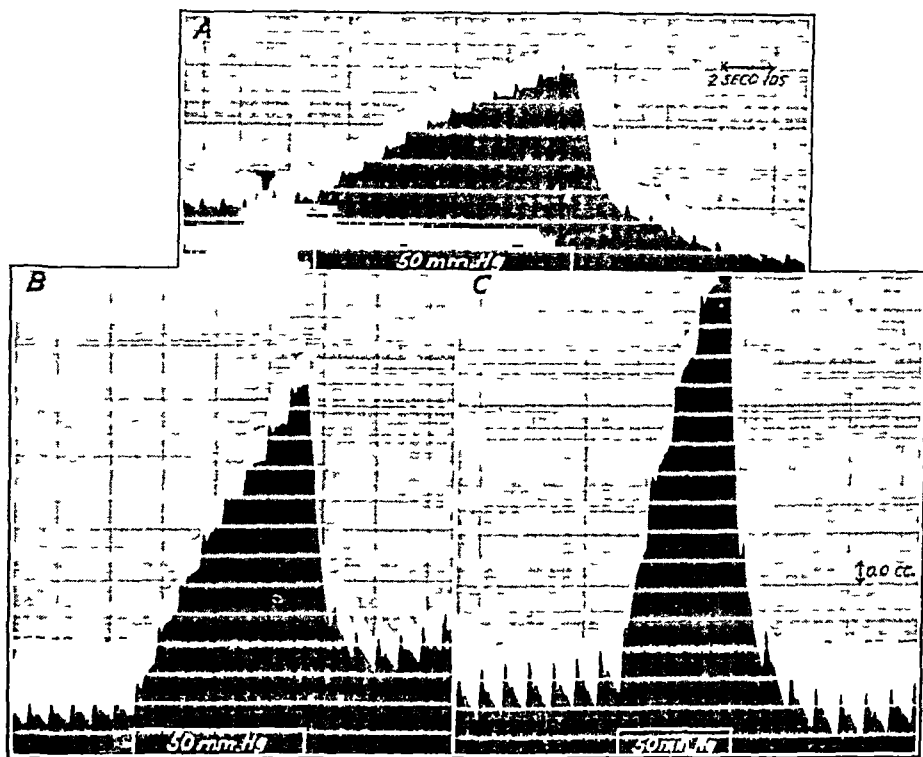


Fig 10—Results of venous congestion test. *A*, after twenty-six minutes' body heating, with occluded circulation in immersed limb, *B*, after release of occlusion, but with continued body heating, *C*, thirteen minutes after release of occlusion, with continued body heating. The same subject was used in figures 8 and 9.

fore follows that unless the occluding pressure is much higher than the systolic pressure determined in an arm before the test, the circulation in the immersed limb (particularly a lower limb) will be reestablished.

There can be little doubt, therefore, from the results of our investigations, that it is the return of the heated blood into the general circulation which produces reflex vasodilatation. There is no need to

⁸ Alam, M., and Smirk, F. H. Observations in Man upon a Blood Pressure Raising Reflex Arising from the Voluntary Muscles, *J. Physiol.* 89: 372, 1937.

invoke the assistance of any reflex nervous mechanism, as suggested by Duthie and Mackay.³ The warmed blood acts on the thermosensitive centers in the hypothalamus, as Uprus and his co-workers pointed out, it is the gradient, or the rate of the rise, which initiates the relaxation

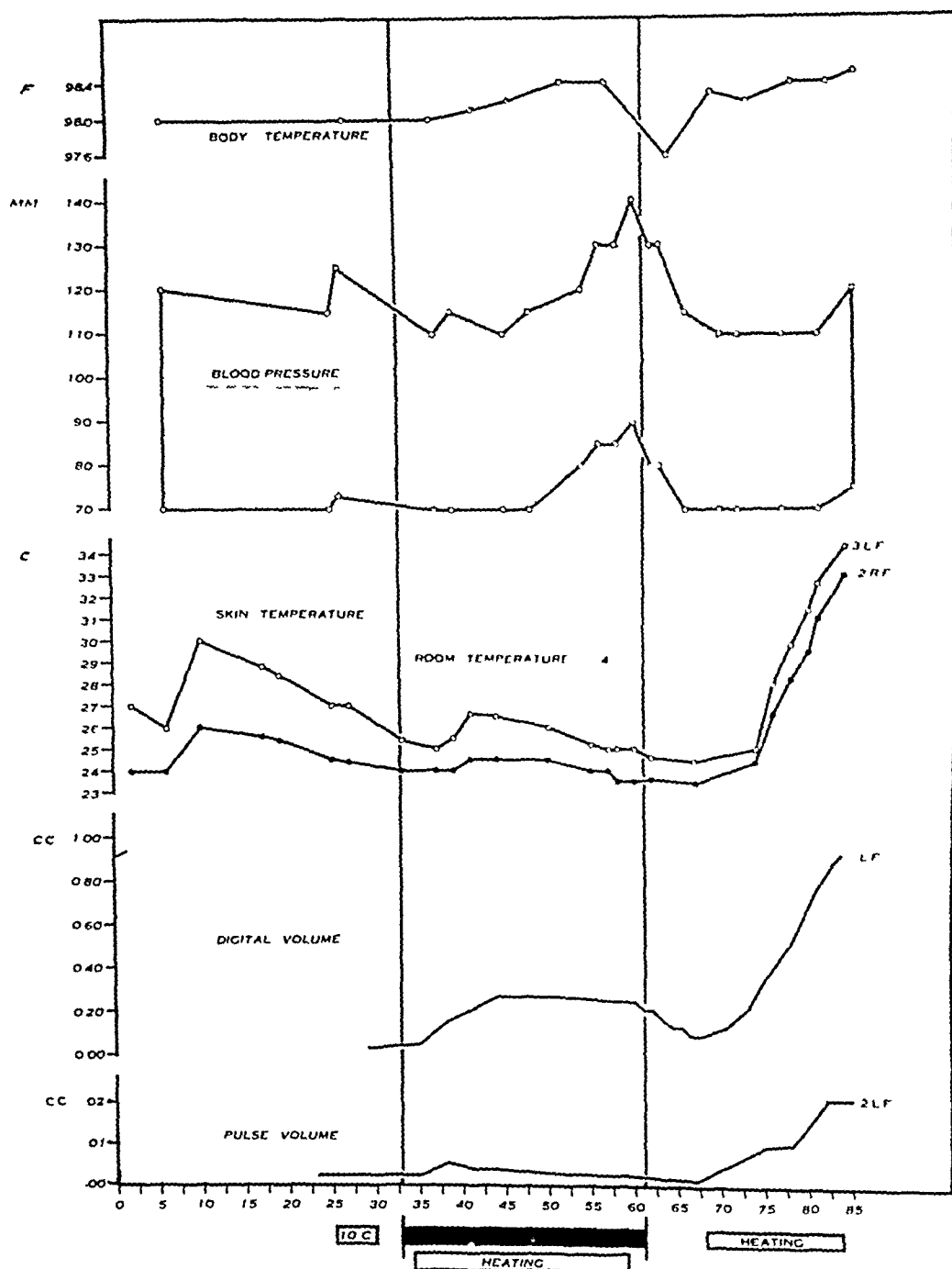


Fig 11—Graph prepared from continuous plethysmogram, demonstrating blood flow through the second left finger, skin temperature of the third left and second right fingers, and blood pressure, while the lower occluded limbs were immersed in water of 45 C for twenty-eight minutes. Note increase in blood pressure, failure to obtain vasodilatation while circulation through the lower limbs was occluded (black area indicates occlusion) and prompt dilatation on reimmersion of lower limbs and release of occlusion.

Clinical Significance of the Humoral Mechanism in Reflex Vasodilatation Produced by Body Heating—Recognition of the significance of the humoral mechanism is not only of academic, but of great clinical, importance. In order to obtain a sufficient temperature gradient, the blood flow through the immersed extremity must be good, as otherwise

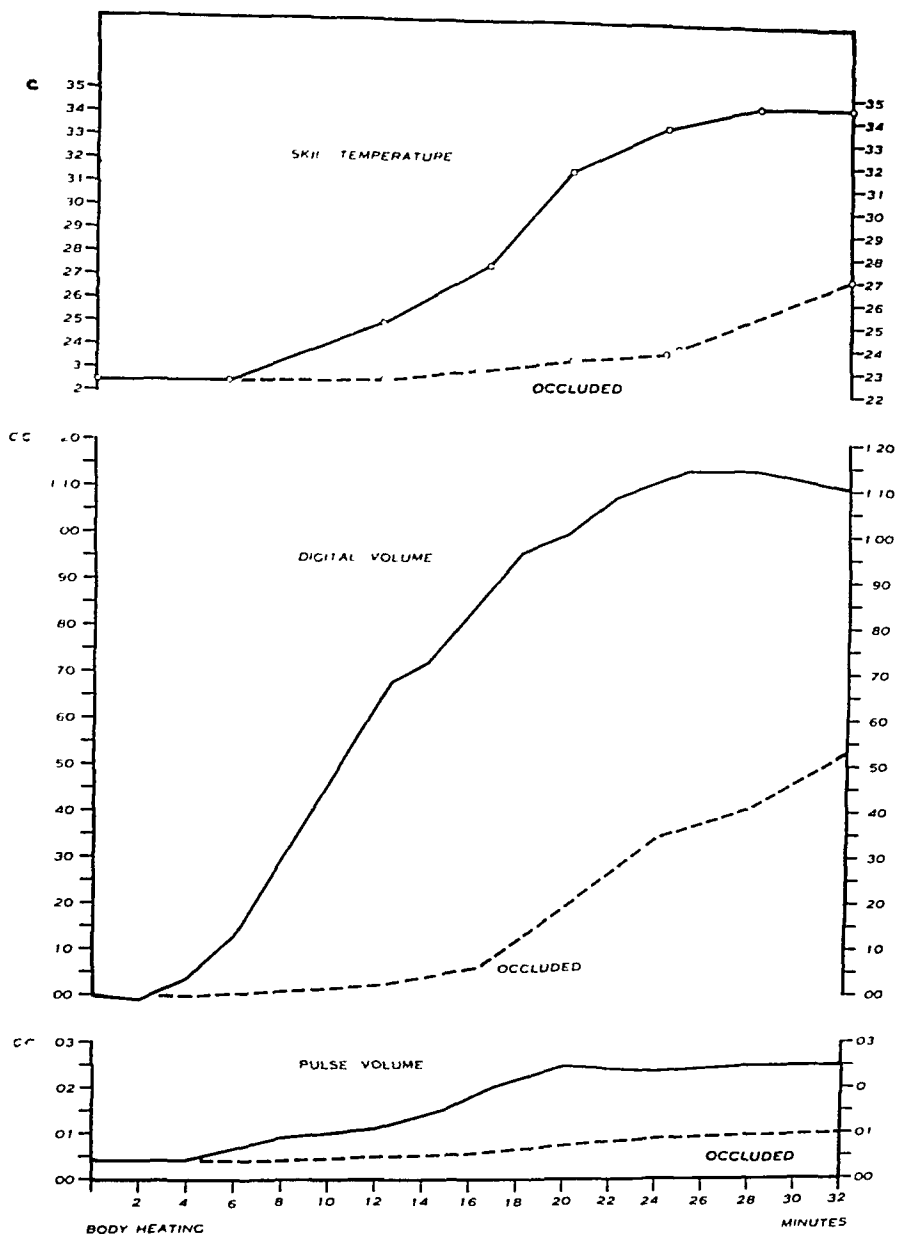


Fig 12—Graph prepared from continuous plethysmogram of first left toe. Digital volume, pulse volume and skin temperature were continuously recorded while body heating was carried out (a) by immersion of the normal left arm (uninterrupted lines), and (b) by immersion of the right arm, with severed axillary artery (interrupted lines). Note failure to produce full reflex vasodilatation in the left leg by immersion of the right arm, but completely normal response following immersion of the left arm.

little warmed blood will be returned into the general circulation, and body heating will have but little effect. It stands to reason that immersion of a limb with arterial occlusion, from any cause, will have the same result as immersion of a limb with experimental occlusion. There will be no, or but little, reflex vasodilatation in a completely normal limb when the immersed limb shows organic occlusion of its vessels, this is an important point which, to our knowledge, so far has not been appreciated by investigators in this field. It stands to reason that the limb being immersed should have a normal circulation; otherwise, the validity of the results of the body heating test is questionable. A typical example is illustrated in figure 12. The data are for a young Negro with a completely normal cardiovascular system, but who had had his right axillary artery accidentally severed. The blood flow in all limbs except the right arm was completely normal. Body heating was carried out by immersing the left arm, and subsequently the right arm, in water of 45 C for thirty minutes. The blood flow in the right leg was tested. The uninterrupted lines in figure 12 indicate the result of the test with reference to immersion of the left arm. After four minutes' body heating, both digital volume and pulse volume (first left toe) increased, and after six minutes, the skin temperature (second left toe) did likewise. In only twenty minutes, the pulse volume in the right limb had reached values well above the minimum vasodilatation level (0.02 cc). Within twenty-six minutes, the digital volume rose simultaneously more than 1.0 cc and the skin temperature reached the normal vasodilatation level of 34 C (93.2 F). Thus, all values indicated that the blood flow in the right leg was completely normal. When the right arm was immersed, the picture was vastly different (interrupted lines, fig 12). Dilatation also took place in the right leg, but it was much more gradual, and after thirty minutes' body heating, the pulse volume did not even register 0.01 cc. The skin temperature had only reached 27 C (80.6 F), and the digital volume had risen by only 0.4 cc (fig 12). The results, then, indicate clearly the importance of an adequate return of heated blood in order to induce vasodilatation. The blood flow in the immersed extremity has to be good. Unless the investigator is aware of this pitfall, he may draw incorrect conclusions from such tests carried out on routine clinical examination. With organic occlusion of the arteries in the immersed extremity, the amount of heated blood returned will be insufficient to produce the necessary gradient, and dilatation may be incomplete or absent. The vessels of the tested extremity at the time may be absolutely normal, yet the diagnosis of arterial disease may be made. Indeed, in the majority of cases of organic arterial disorders in any vascular clinic, involvement of all extremities to varying degrees is the rule.

Thus, failure of the immersion method to produce reflex vasodilatation may not mean organic occlusion of the limb tested but may reflect interference with the blood flow in the immersed extremity. Therefore, nothing factual may be revealed about the vessels in the extremity under examination in such cases. Obviously, the error is not inherent in methods producing dilatation by surgical interruption of sympathetic pathways (paravertebral block or spinal anesthesia) or by direct application of heat. In many of our tests, when there is the slightest doubt as to the effectiveness of reflex body heating, we accordingly follow up reflex vasodilatation by the direct application of heat. One of the prerequisites for a successful body heating test, therefore, is that the blood flow in the immersed extremity be normal.

COMMENT

Sewall and Sanford⁹ observed that immersion of one hand in hot water increased the blood flow in the other and thereby established the principle of reflex dilatation, i. e., induction of vasodilatation in one extremity by the application of heat to another. Winkler¹⁰ demonstrated flushing of the ear of a rabbit when the hindquarters were immersed in hot water. In 1906, Muller¹¹ first suggested that immersion of one extremity in warm water, in conjunction with limb plethysmography, might be used with advantage in the diagnosis of peripheral vascular diseases, particularly in distinguishing between Raynaud's disease and organic arterial occlusion. Stewart¹² found that immersion of one arm in hot water increased the blood flow in the opposite extremity by measuring calorimetrically the loss of heat in the latter.

Babinsky and Heitz¹³ attempted, with the oscillometer, to distinguish between occlusion and spasm before and after the immersion of one extremity in a hot bath, and Barcroft and Marshall¹⁴ found that the minute volume of a person exposed to warmth is raised by 3 to 4 liters,

9 Sewall, H., and Sanford, E. Plethysmographic Studies of the Human Vasomotor Mechanism, *J. Physiol.* **11** 179, 1890.

10 Winkler, F. Studien über die Beeinflussung der Hautgefäße durch thermische Reize, *Sitzungsber. d. Akad. d. Wissensch. Math.-naturw. Cl. (Abt. 3)* **111** 68, 1902.

11 Muller, O. Zur Funktionsprüfung der Arterien, *Deutsche med. Wchnschr.* **32** 1531 and 1577, 1906.

12 Stewart, G. N. Studies on the Circulation in Man. The Measurement of the Blood Flow in the Hands, *Heart* **3** 33, 1911.

13 Babinsky, J., and Heitz, J. Obliterations arterielles et troubles vasomoteurs d'origine réflexe ou centrale, *Bull. et mem. Soc. med. d. hôp. de Paris* **40** 570, 1916.

14 Barcroft, J., and Marshall, E. K. Note on the Effect of External Temperature on the Circulation in Man, *J. Physiol.* **58** 145, 1923.

a quantity which is probably a rough measure of the increased blood flow through the skin. In 1931, Lewis and Pickering¹⁵ demonstrated that reflex vasodilatation in the digits of the upper extremity was dependent on the integrity of the sympathetic nervous supply and, therefore, could not be obtained in an extremity which had previously been sympathectomized.

Unfortunately, Muller's suggestion of using reflex vasodilatation as a clinical test was lost sight of, to Gibbon and Landis⁶ goes the credit of having drawn our attention anew to this simple procedure. They pointed out its great value as a routine test in the study of the peripheral circulation in general, and of peripheral vascular diseases in particular. They suggested that the mechanism of the reflex vasodilatation was brought about by the return of heated blood from the extremity, and not by a reflex nervous mechanism. Gibbon and Landis, in 1932, and Pickering and Hess¹⁶ noted that vasomotor relaxation was produced with greater ease in the upper extremities, as a result of the immersion of the lower extremities in warm water, than when the process was reversed. In this respect, it is interesting that vasodilatation, as produced by injection of typhoid vaccine or by the intra-arterial or intravenous injection of methacholine chloride U. S. P. (mecholyl chloride®) was greater in the fingers than in the toes (Horton, Roth and Adson¹⁷, Allen and Crisler¹⁸).

Gibbon and Landis produced reflex vasodilatation in the lower extremities by immersion of both forearms in water of 42 to 45 C. They stated the belief that the procedure was necessary, since they could not produce complete relaxation of the blood vessels in the feet by immersing only one hand, as far as the wrist, into water of that temperature. Our experience shows that complete vasodilatation readily results from immersion of one arm, to a point about 6 inches (15 cm.) above the elbow, provided the subject is covered with a woolen blanket to prevent the dissipation of heat (Goetz^{5b,d,c}).

In 1940, however, Duthie and Mackay published a lengthy paper, in which the data contradicted those of Gibbon and Landis and, in fact,

15 Lewis, T., and Pickering, G. W. Vasodilatation in Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* **16** 33, 1931.

16 Pickering, G. W., and Hess, W. Vasodilatation in the Hands and Feet in Response to Warming the Body, *Clin. Sc.* **1**:213, 1933-1934.

17 Horton, B. T., Roth, G. M., and Adson, A. W. Observations on Some Differences in Vasomotor Reactions of Hands and Feet, *Proc. Staff Meet., Mayo Clin.* **11** 433, 1936.

18 Allen, E. V., and Crisler, G. R. The Results of Intra-Arterial Injection of Vasodilating Drugs on the Circulation. Observations on Vasomotor Gradient, *J. Clin. Investigation* **16** 649, 1937.

of all previous investigators. Their experiments seemed to prove that heating of a limb the circulation of which had been cut off by a sphygmodynamometer cuff inflated to a pressure of 200 to 250 mm or over still produced reflex vasodilatation in the other limbs. They came to the conclusion that vasodilatation was the result of a nervous reflex and suggested that the afferent impulses concerned might arise from the stimulation of the nerve endings in cutaneous blood vessels. However, they experienced considerable difficulty in tracing the exact nervous pathways and stated that the afferent impulses did not run in the sympathetic nerves or in the spinothalamic tract.

The present investigations do not support any of Duthie and Mackay's conclusions, but they confirm that reflex vasodilatation is due to the action of heated blood, returning from the immersed extremity, on the thermosensitive centers in the hypothalamus. It is difficult to see how Duthie and Mackay obtained their results. It appears possible that the occlusion pressure used in their experiments was not sufficiently high to interrupt the circulation through the immersed limb. They used pressures of 200 mm or higher throughout. There is a possibility that that pressure—at least in some experiments—was not sufficiently high, particularly if the limbs immersed were the lower extremities. We demonstrated by plethysmographic methods that a considerably higher pressure was required to interrupt the arterial circulation in the lower limbs than was required in the upper limbs (the pressure in our experiments was up to 60 mm higher than the systolic pressure, as obtained in the upper limbs by clinical methods). In addition, we demonstrated that immersion of the occluded limb resulted in a considerable rise in blood pressure, which rapidly returned to normal on freeing of the circulation. The latter observation finds support in the work of Alam and Smirk.⁸ They demonstrated that an increase of systolic blood pressure up to 85 might be obtained in normal human subjects by accumulation of metabolites in voluntary muscles. They demonstrated that the phenomenon was due to a reflex which was set up by nerve impulses arising from the voluntary muscles, but which was not necessarily associated with pain or discomfort, the reflex rise in blood pressure which occurred when metabolites accumulated in the voluntary muscle on exercise was therefore due not only to the pain. Although Alam and Smirk produced the blood pressure-raising reflex by exercising occluded voluntary muscle, it stands to reason that immersion of an occluded arm in warm water for thirty minutes would cause the same waste products and metabolites to accumulate. Therefore, the same blood pressure-raising reflex would come into play, as indeed we demonstrated in our experiments.

Hence, in order to occlude and keep occluded the circulation through the lower extremities, full consideration has to be made of the facts that (1) a pressure 50 to 60 mm higher than the systolic pressure, determined clinically in the arm, is required for occlusion of the blood flow through the lower limbs, and that (2) during the course of the test a considerable rise in systolic blood pressure is to be expected. Therefore, a pressure of 200 to 250 may not be sufficient to interrupt, and keep interrupted, the circulation through the immersed lower limbs.

In the light of these investigations, the results obtained by Duthie and Mackay are extremely illuminating. They found that they failed to produce dilatation in 6 of 11 experiments in which the immersed and occluded limb was an arm. However, in only 1 of 7 experiments did they fail to obtain vasodilatation when the immersed and occluded limb was a leg. These findings strongly support our suspicion that the reason for their obtaining vasodilatation by immersion of an occluded limb was failure to keep the circulation occluded, which one would expect to occur first when the lower limbs were used.

In the experiments reported, therefore, we insisted on determining beforehand, by plethysmographic means, the pressure which would assure complete arterial occlusion. It was demonstrated, in the case of 2 subjects who showed reflex vasodilatation on immersion of an occluded limb in water of 43 C, that application of higher pressure abolished the response. Subsequently, it was demonstrated that the original pressure was not sufficient to abolish the return of heated blood from the extremity. Indeed, Pickering estimated that a rise of 0.01 to 0.04 C (0.018 to 0.072 F) in body temperature was sufficient stimulus for the thermosensitive centers in the hypothalamus to initiate peripheral vasodilatation. There is no reason, therefore, to assume that a nervous reflex mechanism is involved in the vasodilatation produced by body heating. Had such a nervous reflex mechanism existed, it would have been difficult to understand how, in the case of 1 of our patients with a transverse lesion at the sixth thoracic segment, complete vasodilatation in the upper limbs occurred on immersion of the lower limbs. Similarly, Uprus, Gaylor and Carmichael² demonstrated that reflex vasodilatation in the upper extremities was easily obtained by immersion of the lower extremities in the case of patients in whom there was no nervous connection between the legs and the rest of the body. Other evidence tallies with this view. Kahn¹⁹ and Moorehouse²⁰ found that warming of the blood in the carotid

¹⁹ Kahn, R. H. Ueber die Erwärmung des Carotidenblutes, *Arch f Anat u Physiol*, 1904, supp., p. 81.

²⁰ Moorehouse, V. W. K. Effect of Increased Temperature of the Carotid Blood, *Am J Physiol* 28:223, 1911.

artery of the dog or rabbit will cause vasodilatation of the skin vessels of the pads of the paws, as well as sweating Hill²¹ reported that a patient, made to sweat by moving about in a hot room, ceased sweating when the hands were immersed in cold water. However, when the circulation of the hands was arrested beforehand, cooling of the hands had no effect on the sweating.

Recognition of the fact that vasodilatation is produced by heated blood is of clinical importance. When the arm immersed shows organic arterial occlusion, conditions prevail similar to those obtained when the blood flow has been interrupted experimentally. The amount of blood heated is minimal. Therefore, immersion of such an extremity may fail to produce vasodilatation in the other extremities. Indeed, it was demonstrated in our experiments that very misleading results might be obtained when there was any interference with the arterial blood flow through the immersed extremity. The case of a young man with completely normal circulation, but whose axillary artery had accidentally been severed, is reported, when the circulation through the lower extremities was tested by immersion of the arm with the normal blood flow, completely normal vasodilatation occurred, but when the arm with the severed axillary artery was immersed, vasodilatation was greatly diminished in the lower extremities, and simulated that in organic arterial disease. Indeed, in all cases of persons with thromboangitis obliterans or arteriosclerosis, arterial flow in the immersed limb has to be considered when testing the peripheral circulation by means of body heating tests, since all extremities are involved, to varying degrees, in these conditions. By carrying out the tests indiscriminately, the investigator may come to completely wrong conclusions. Failure of the immersion method to produce reflex vasodilatation may not necessarily mean organic occlusion in the limb tested, but may actually reflect organic occlusion of the immersed extremity, revealing nothing about the vessels of the limb under examination. Accordingly, it is emphasized that in many cases, another method of producing complete relaxation of the peripheral vessels is needed. One method, which can be applied to great advantage when plethysmographic methods of measuring the peripheral blood flow are used, is the local application of heat, in many a test, we follow up reflex vasodilatation with the direct application of heat. That occlusion of the immersed extremity plays an important part in determination of the degree of reflex vasodilatation was borne out also by the experiments of Uprus, Gaylor and Carmichael,² who demonstrated that it was the gradient, or the rate of rise in body temperature, rather than the actual body temperature or temperature of the blood, which initiated reflex vasodilatation. It stands to reason

21 Hill, L. The Capillary Blood Pressure, *J. Physiol.* **54** 244, 1921

that when there is interference with the peripheral blood flow of the immersed extremity, the gradient is affected first, although a rise in the actual blood temperature, sufficient to initiate vasodilatation, may be attained eventually

SUMMARY AND CONCLUSIONS

1 Immersion of one upper extremity or of both feet in water of 45 C for thirty minutes, with prevention of the dissipation of heat from the body, normally results in reflex dilatation in the other extremities

2 The reflex vasodilatation is obtained in the upper extremities by immersion of the feet in the case of patients with high transverse spinal lesions (involving the sixth thoracic segment)

3 Vasodilatation is not obtained when the circulation through the immersed extremity is interrupted. Therefore, reflex vasodilatation is dependent on the return of heated blood, which acts on the thermosensitive center in the hypothalamus, and the mechanism of reflex vasodilatation from body heating is not nervous in origin

4 The pressure required for occlusion of the arterial circulation of the lower limbs by means of a cuff fixed on the thigh is considerably higher than that required for occlusion of the circulation to the hand with a cuff above the elbow. It is therefore confirmed that the "blood pressure" in the lower limbs is higher than in the upper

The method of measuring the blood pressure objectively, and, if necessary, in two limbs simultaneously, with the digital plethysmograph, is described

5 The higher "blood pressure" in the lower limbs is due to the larger volume of surrounding muscle. When the cuff is fixed above the ankle, the pressure required for occlusion of the blood flow is considerably lower than that required when the cuff is fixed at the thigh

6 Heating of an occluded limb produces a considerable rise in blood pressure, owing to the accumulation of metabolites in the muscle. Because of this, and because of the high "blood pressure" in the lower limbs, an extremely high occlusion pressure is required to keep the circulation in the lower limbs interrupted during the period of immersion

7 Failure to keep the circulation through the lower limbs occluded is considered the main reason why some authors obtained reflex vasodilatation on immersion of a limb in which the circulation was thought to be occluded

8 Recognition of the "humoral" mechanism underlying reflex vasodilatation as obtained by body heating is of clinical importance. The

blood flow through the immersed limb must be good, otherwise, an insufficient amount of heated blood is returned and reflex vasodilatation is minimal or absent. The method, therefore, gives misleading results when there is organic arterial disease of appreciable degree in the immersed limb. The results in such a case reflect the circulation in the immersed extremity, rather than in the one studied.

The findings in a case of severed axillary artery are described to illustrate the importance of good circulation in the immersed extremity for satisfactory assessment, by the immersion method, of the condition of the arterial tree in other limbs.

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FAMILIAL PERIODIC PARALYSIS

Report on Two Families, with Observations on the Pathogenesis of the Syndrome

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TRANSIENT paralysis of skeletal muscle without other neurologic abnormality is an interesting syndrome which has been recognized and observed clinically for over a hundred years. Although in comparatively recent times the disorder has been reported in the course of other diseases, notably thyrotoxicosis,¹ and in diabetic coma,² in by far the larger number of cases reported it existed as a familial trait, unassociated with other disease.

During a typical attack, the patient shows flaccid paralysis of the skeletal musculature, loss of all deep reflexes and electrical excitability of the muscles, with complete preservation of sensation and mental function. The disease usually does not manifest itself until puberty, the attacks of paralysis are characteristically noted by patients when they awaken in the early morning hours. Weakness lasts from a few hours to a few days, spares all musculature above the neck and disappears completely without residual effects.

In 1941, Talbott,³ in his excellent monograph on the subject, reviewed the literature and stated that up to that date slightly over 400 cases had been reported, which number indicates that the disease is a comparative rarity. About 80 per cent of cases reported are familial, but many of the nonfamilial cases differ in no other way from the familial ones. A small number of cases have been associated

The case of patient A L was studied in the neuropsychiatric service of the United States Naval Hospital, San Diego, Calif.

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1 Dunlap, H F, and Kepler, E J. Occurrence of Periodic Paralysis in the Course of Exophthalmic Goiter, *Proc Staff Meet, Mayo Clin* 6 272 (May 6) 1931.

2 Holler, J W. Potassium Deficiency Occurring During Treatment of Diabetic Acidosis, *J A M A* 131 1186 (Aug 10) 1946.

3 Talbott, J H. Periodic Paralysis. A Clinical Syndrome, *Medicine* 20 85-143 (Feb) 1941.

with myopathy,⁴ with migraine⁵ and, as has been pointed out, with thyroid disease. These facts gave rise to various theories as to the pathogenesis of the disease,⁶ but major progress was made in the understanding of the disorder in 1937 and 1938, when it was reported from various laboratories that many attacks of paralysis were accompanied with a drop in serum potassium and recoveries, by a corresponding rise.⁷ Administration of potassium chloride by mouth greatly hastened termination of the paralysis, present day therapy is based on that discovery. Careful balance studies, reported recently by Danowski, Elkington and Winkler,⁸ have substantiated the observation that the potassium lost from the serum is not excreted but rather enters the intracellular portion of body tissues. However, whether the paralysis is caused by the low serum potassium level, by chronic deficit of potassium in muscle, or by a disorder of hepatic or muscular glycogenesis or of permeability of muscle cells is one of the major problems of the disease.

In the present study, the hitherto unreported case of a boy of 17 with classic familial periodic paralysis, subject to attacks usually not oftener than once every two months, was investigated. It has long been known that in cases of this disorder, administration of excess carbohydrate by mouth or injection of epinephrine or insulin is effective in bringing on attacks.^{6b} Of these stimuli, the most consistently useful has been carbohydrate. Gammon, Austin, Blithe and Reid,^{7c} however, reported success in precipitating attacks by causing excessive

4 Biemond, A, and Daniels, A P. Familial Periodic Paralysis and Its Transition into Spinal Muscular Atrophy, *Brain* **57** 91 (June) 1934

5 (a) Holtzapple, G E. Periodic Paralysis, *J A M A* **45** 1224 (Oct 31) 1905. (b) Machlachlan, T K. Familial Periodic Paralysis. A Description of Six Cases Occurring in Three Generations of One Family, *Brain* **55** 47 (March) 1932

6 (a) Machlachlan.^{5b} (b) Shinosaki, T. Klinische Studien über die periodische Extremitätenlahmung, *Ztschr f d ges Neurol u Psychiat* **100** 564, 1925-1926. (c) Wolf, A. The Effective Use of Thyroid in Periodic Paralysis, *New York State J Med* **43** 1951 (Oct 15) 1943

7 (a) Aitken, R S, Allott, E N, Castleden, L I M, and Walker, M B. Observations on a Case of Family Periodic Paralysis, *Clin Sc* **3** 47 (July) 1937. (b) Pudenz, R H, McIntosh, J F, and McEachern, D. The Role of Potassium in Family Periodic Paralysis, *J A M A* **111** 2253 (Dec 17) 1938. (c) Gammon, G D, Austin, J H, Blithe, M D, and Reid, C G. The Relation of Potassium to Periodic Family Paralysis, *Am J M Sc* **197** 326 (March) 1938. (d) Feirebee, J W, Atchley, D W, and Loeb, R F. A Study of Electrolyte Physiology in a Case of Family Periodic Paralysis, *J Clin Investigation* **17** 502 (July) 1938

8 Danowski, T S, Elkington, J R, and Winkler, A W. Exchanges of Sodium and Potassium in Familial Periodic Paralysis, *J Clin Investigation* **27** 65 (Jan) 1948

diuresis in their patient and "washing" potassium out of the body. In the case here reported, an effort was made to contribute further data on the relation of the paralysis to the ingestion of carbohydrate, and on the factor responsible for the weakness (abnormality in serum electrolytes or local muscular disorder). The results relate to effective provoking stimuli for attacks, time interval from stimulus to attack, and from administration of potassium chloride to recovery, serum potassium level during attacks, and a test for abnormal muscular response to cold.

RESULTS IN CASE 1

CASE 1 (A. L.)—*Effective Stimuli*—Administration of 200 Gm of dextrose by mouth produced paralysis or appreciable paresis in eight of nine attempts. One attempt was made to induce an attack by injection of 25 units of regular insulin at 6:30 p.m., two hours after an average meal. The patient was awakened at 3 a.m., by which time paralysis was expected, his muscle power was normal, and he was given 100 Gm of dextrose by mouth. Four hours later, pronounced paresis was evident in all four extremities.

Two attempts were made to precipitate attacks by means of water diuresis. The method described by Gammon and others^{7c} (administration of 350 cc of water every fifteen minutes for three hours) was employed. Both trials were made with the patient in fasting condition, one was made from 7 to 10 p.m. and another, from 3 to 6 p.m. Neither attempt resulted in paralysis within forty-eight hours.

Time Interval—It was noted that spontaneous attacks, as is so frequent in this disease, became apparent in the early morning hours, some eight to twelve hours after the "heavy meal," to which they were attributed by the patient. On four occasions, the patient was given 100 to 200 Gm of dextrose by mouth at 6 p.m., shortly after an evening meal. On two occasions, the meal contained 175 Gm of carbohydrates, and on two other occasions it was a normal hospital meal. In each instance, the patient was awake and asymptomatic for two to three hours after administration of the dextrose and awoke from eight to twelve hours after administration, with a typical attack of greater or less severity.

An attempt was made to determine whether it was actually the sleep or rather the long period of inactivity and fasting which caused the attacks to appear characteristically in the early morning hours. (The possibility that the light-darkness cycle itself had some relation to the onset was not investigated.)

The patient was on four occasions given 200 Gm of dextrose by mouth after a normal breakfast at 8 a.m. and kept in bed, with omission of all food, including the noon meal. He was instructed to remain quiet. On the first occasion, no paralysis was evident by 5:30 p.m., and the test was terminated. On another occasion, the patient showed pronounced paresis of arms and legs after eight hours (the value of the trial was somewhat vitiated by the fact that the patient had neglected to make known that he had a "touch of weakness" before the test began, nevertheless, he volunteered the information that it was the first time he had experienced onset of weakness during the day). The third trial resulted, within six hours, in moderate asymmetric weakness, chiefly of extensors of wrists and feet and of the quadriceps muscle (the patient's usual pattern). Despite his partial recovery from the weakness during the early evening, given exercise alone with no medication, he awoke the next morning with far more profound paralysis.

of both arms and legs. On the fourth trial, throughout the entire waking day (fourteen hours) after administration of dextrose, the patient was asymptomatic, only to awaken the next morning with a severe attack, accompanied by a fall of serum potassium to 10.6 mg per hundred cubic centimeters.

Serum Potassium—Determinations of serum potassium were done by the flame photometer method at the height of each of four attacks of the disease, all of which were noted on the patient's awakening in the morning, the blood was drawn two to three hours afterward. In two attacks, the level was 16 mg (a low normal value). Both the latter were mild attacks, with preservation of fair muscle power in one or all limbs and patchy distribution of paralysis. The potassium values in the other two attacks were 10.6 and 10 mg, respectively. In both these attacks, the patient showed much more profound paralysis.

Potassium chloride (8 Gm) was administered by mouth at the height of paralysis in seven attacks, usually in the morning, a few hours after the paralysis was discovered. In each instance, improvement was noted in one-half hour, but in the severe attacks (four in number, and in one of which the level of serum potassium was 10 mg) full recovery did not return for three hours. In milder attacks, recovery occurred in one to two hours. In two attacks, recovery two hours after administration of 8 Gm of potassium chloride seemed so slow that a second dose was given.

During one severe attack, the administration of potassium chloride intravenously, as reported by Pudenz and his co-workers,^{7b} was carried out, 100 cc of a 1 per cent solution was injected into the antecubital vein over a period of ten minutes. Results paralleled those of Gass, Cherkasky and Savitsky⁹ in that negligible increase in strength was noted during fifty minutes of observation. Pain persisted along the course of the vein. After the period of observation, 8 Gm of potassium chloride was given by mouth, with the usual gradual improvement over the next two hours.

Abnormal Response to Cold—On four occasions, the patient was tested for reaction of the skeletal musculature to cold. The procedure, that used by Zabriskie and Frantz,¹⁰ was immersion of the forearm to a point above the elbow, in water kept at 10 to 14 C, for a period of thirty-five minutes. The patient held his hand motionless, in a loose fist. On withdrawal of the arm, ability to flex and extend fingers and activity of the biceps reflex were observed at five minute intervals for a half hour. The first two trials revealed that the patient's fingers were almost immobile immediately on withdrawal from the water, the flexor activity returned first, being almost normal at the end of fifteen minutes, but extensors of the phalanges remained observably weak, even at the end of a half hour. The last two trials were made with 2 control subjects undergoing the same procedure. In the control subjects, weakness of the musculature followed the same pattern, but flexor power returned within one minute, and extensor power showed considerable improvement in three minutes, barely observable impairment was present at ten minutes, and complete recovery occurred in fifteen minutes.

9 Gass, H., Cherkasky, M., and Savitsky, N. Potassium and Periodic Paralysis. A Metabolic Study and Physiological Considerations, *Medicine* 27: 105 (Feb.) 1948.

10 Zabriskie, E. G., and Frantz, A. M. Familial Periodic Paralysis. Report of a Case, *Bull. Neurol. Inst., New York* 2: 57 (March) 1932.

In the patient, the biceps reflex was unobtainable immediately after the test. It had returned to normal in ten minutes. In the controls, the biceps reflex was obtainable, but much diminished as compared to the opposite side, about the same period as for the patient was required for the reflex to equal that of the untested arm.

REPORT ON TWO FAMILIES

FAMILY A—Inasmuch as patient A L was a member of an apparently unreported large family (family A, chart 1) which was gathered in a small geographic area, I was able to interview 9 persons who had a history of manifestations of the disease. It is felt that the amazing variety in these clinical histories, in addition to the patients' interesting observations as to the results of use of potassium chloride,¹¹ justifies the addition of the case reports. The number of persons indicated in the genealogic history (chart 1) as suffering from the

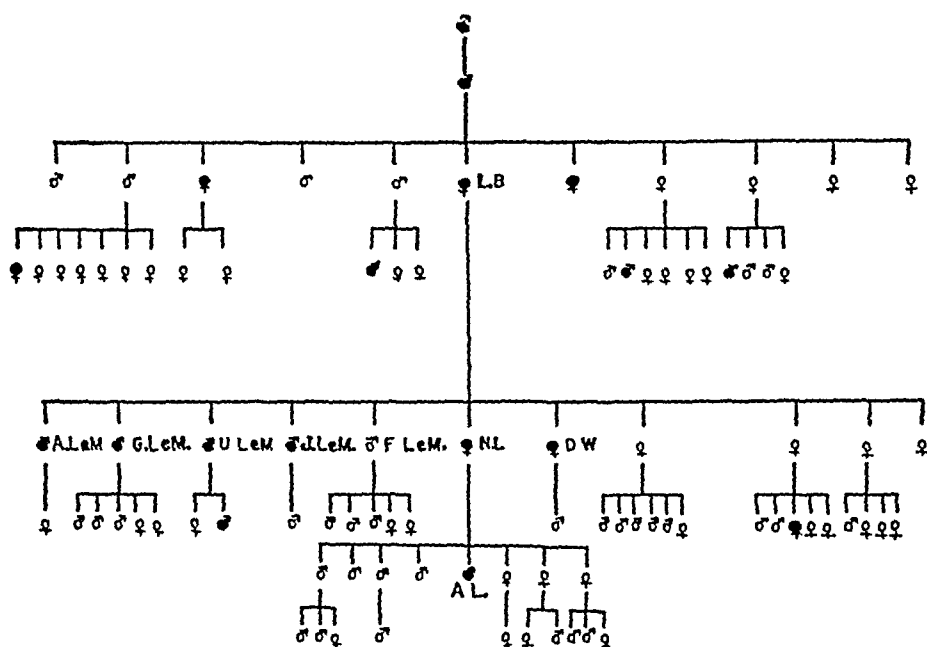


Chart 1—Family A. Black symbols indicate persons known to have manifested periodic paralysis.

disease is undoubtedly inaccurately small, for two reasons. Minor manifestations of the disease in fairly distant relatives probably were known to the patients interviewed, and many relatives in A L's generation were children and thus had not arrived at the age when the disease would be expected to become manifest.

FAMILY B—Family B (chart 2) was discovered as the result of a chance observation by A L, concerning the existence of the disease in an acquaintance of his. Several members of the family were interviewed, no attacks were witnessed, but from the description of the attacks and of the response to potassium chloride, the disease was without doubt familial periodic paralysis. The family

¹¹ Members of family A had "heard of" potassium chloride from a distant relative as a remedy for their malady, and various members had been using it empirically and without medical supervision during the previous five years. One member of family B evidently had the disease diagnosed in a military hospital, and potassium chloride was recommended.

lived within 10 miles (16.1 km) of family A, but as far as either family knows they are unrelated

CASE 1 (FAMILY A)—A L, the original patient to be observed, was a boy of 17, with a condition previously diagnosed as hysteria. On eliciting the family history, familial periodic paralysis was suspected, and during the first observed attack the characteristic triad of flaccid paralysis and loss of deep reflexes and of muscular excitability was demonstrated. The onset of the disease in this patient was at the age of 10 or 11, at which time the attacks were quite frequent, usually occurring oftener than once per month. During the last two years, however, attacks had rarely occurred oftener than once every two months. As a rule there were no prodromes, the patient would awaken about 3 a.m. and discover that he was unable to turn over in bed. He would usually return to sleep and awaken again in the morning with full or partial paralysis. Motion of the affected limbs would hasten recovery, which would occur within a period of a few to forty-eight hours. There was no disturbance of sensation, mental functions or digestion, but usually there was anuria during paralysis. A heavy evening meal usually preceded the attack, but one attack had occurred in the afternoon, while the patient was sitting in a motion picture theater. The degree of paralysis varied all the way from minimal weakness to full paralysis of one, two, three or four limbs. There was no other significant history of disease. Physical

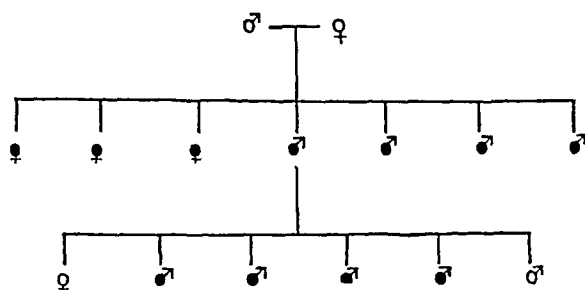


Chart 2—Family B. Black symbols indicate persons known to have manifested periodic paralysis.

examination between attacks revealed a well nourished, well developed, alert young man, showing no physical or neurologic abnormalities. Reflexes were brisk and equal, no pathologic reflexes were present. The blood pressure was 120 systolic and 74 diastolic.

CASE 2 (FAMILY A)—N L, the mother of A L, was 44. The onset of the disorder occurred in her teens, with only one attack in the whole history that progressed beyond a mild weakness of the arms. Attacks were usually preceded by a heavy meal or a late supper and were noted on the patient's arising in the morning and dissipated by exercise. There were no prodromes, no relation to cold or to emotional states, and no sequelae or associated disorders. Attacks had ceased spontaneously nine years before, the patient was taking no medication. Physical examination revealed a moderately obese middle-aged woman with no significant physical findings. The blood pressure was 128 systolic and 80 diastolic.

CASE 3 (FAMILY A)—U LeM, a man of 40, was a sibling of N L. The patient could remember only two periods of weakness during his entire life. These were not instances of full paralysis, but were described as "touches" of the disease, in both arms and legs, resulting in mild asthenia, and accompanied by anuria for the period of weakness (approximately a day).

CASE 4 (FAMILY A)—J LeM, an obese, adolescent boy of 14, was the son of U LeM and a cousin of A L. He was said to have had a "severe attack," which lasted several hours, at the age of 2. Thereafter he was well up to the age of 11, when he began to have attacks two or three times a week, seemingly precipitated by heavy meals or heavy exercise. Attacks varied from complete quadriplegia to mild weakness of one arm or leg and lasted characteristically from a few hours to a few days. During severe attacks there were anuria and weakness of the voice. Following recovery, the patient's muscles felt "sore."

CASE 5 (FAMILY A)—D W, a woman of 41, was a sibling of N L. The patient had suffered her first attack in early childhood, and thereafter attacks had occurred three or four times a year. Severe attacks had spontaneously ceased three years before, but the patient had since noted occasional mild weakness, which she believed to be a manifestation of the disease. She noted the relation of attacks to previous heavy meals and their possible relation to heavy exercise, but to no other factors. The severe attacks would be the typical quadriplegia and would come on at night. When untreated they would last two to three days, but when muscular effort was forced they would disappear in one-half day. However, the patient discovered that after ingestion of potassium chloride, to terminate an attack or to abort an early attack, maximum benefit occurred with rest, not exercise, and that she recovered within an hour. The patient had begun taking "½ teaspoon" of potassium chloride eight years before, after the evening meal, the attacks ceased altogether about five years after she began to take the drug. She had taken none, however, for the two years previous to this report and had remained free of attacks. In addition to the severe attacks, the patient frequently noticed mild to moderate weakness of one arm or leg, which would be dispelled by vigorous exercise. Such weakness was particularly prone to occur after periods of inactivity. After severe attacks, the patient noted "sore" muscles. There was no history of past disease or associated illness. There were no positive neurologic findings on examination. The blood pressure was 130 systolic and 78 diastolic.

CASE 6 (FAMILY A)—A LeM, 47, was a sibling of N L. An asthenic middle-aged man, he had had his first attack at 17, they had occurred about twice a year up to three years before. Since then he had had no attacks. Eight years before, he had begun taking potassium chloride ("¾ teaspoon") three times a week, as a prophylactic measure. He stated that he noted no diminution in frequency of attacks, but that when he took the drug at the onset of an attack it subsided within an hour, unlike the natural course of the "spell." He related the onset of the attacks to heavy meals and to cold, they usually lasted one to four days and were accompanied with oliguria, constipation and a fall in body temperature of 2 to 3 degrees F (as told him by an attending physician). Monoplegias and diplegias were frequent variants of the classic attack. Use of potassium chloride shortened attacks only, according to the patient, when followed with rest. Without potassium, attacks were shortened by "working them off." The patient displayed a right-sided spastic hemiparesis, with hyperactive deep reflexes and signs of damage to the pyramidal tract. He gave the date of onset of this disorder as three years previously, when he was "poisoned with arsenate of lead" contained in a spray he was using in orange groves, he stated that arsenic was found at that time in his blood and urine. There was no other significant history of disease, and there were no other positive physical findings. The blood pressure was 132 systolic and 78 diastolic.

CASE 7 (FAMILY A)—G LeM was a man of 41. The onset of the illness had occurred when he was 31, attacks occurring two to three times a year. During the year previous to the time of writing, the patient had gained a considerable quantity of weight and had noted coincidental increase in the frequency of the attacks (to about one a week). The attacks also followed "heavy meals," usually awakened him in the hours between midnight and dawn and lasted several hours. He had 5 children, 5 to 18, none of whom had displayed signs of the condition. During the past six months, he had tried using potassium chloride ("½ to 1 teaspoon just as I need it"). He had noted no diminution of frequency of attacks but did state that the drug shortened the period of paralysis, he felt that recovery was quicker when he "kept still for a couple of hours after taking it." There were no positive neurologic findings on examination.

CASE 8 (FAMILY A)—Ja LeM, 32, was a brother of N L. The onset of the illness occurred when he was 12 or 13. Attacks varied from slight weakness, which for a considerable time occurred almost every day, to the generalized paralysis, which came on at night. Not only heavy meals but also severe chilling brought on this patient's attacks, he was in the Army for thirty-nine months and noted an increase in the number of attacks when living in a pup tent. On one occasion, after extreme anger and exertion, an attack came on abruptly and lasted two days. During severe attacks, the patient had difficulty moving his tongue and spoke thickly, on one or two occasions, he had needed artificial respiration. During the previous two years, the patient had started taking potassium chloride, which he stated had shortened his attacks. He had taken 1 to 2 teaspoons "occasionally after a heavy meal," prophylactically, and had had no attacks for the year previous to this report. He felt that remaining quiet after taking the potassium chloride shortened attacks. Physical examination revealed a rather asthenic young man, showing no abnormalities.

CASE 9 (FAMILY A)—L B, 72, was the mother of N L and her siblings. She had had only two attacks of paralysis in her entire life. Both had occurred in her youth and had been classic nocturnal episodes of quadriplegia, lasting three to four hours. (She had observed innumerable severe attacks in her father, who had lived, despite their persistent occurrence, to the age of 95. Some type of paralysis, thought to be the residuum of a stroke, had confined him to a wheelchair for the latter years of his life. He, in turn, had inherited the trait from his father, who was alleged to have had numerous severe attacks.) Aside from a pronounced degree of deafness, L B showed no neurologic abnormalities.

CASE 10 (FAMILY B)—G T, a man of 27, had had his first attack at 17, after which he had had generalized attacks approximately once a month, beginning in the night and lasting one to three days. Eating of large meals was volunteered as a provoking factor in attacks. The onset of the paralysis was always preceded by severe vomiting. For the previous five years, however, attacks had diminished to "slight touches" of weakness. In the previous three years, during most of which time the patient was in the Army (he stated that the disease was recognized in an Army hospital), he had had only one severe attack. During those years he had known of potassium chloride, he had not taken it in a regular prophylactic manner, but only at the onset of an attack. The patient volunteered the information that he had repeated attacks when in high altitudes. No attacks of this patient or of any of his family were seen by me.

OTHER CASES IN FAMILY B—Two unaffected siblings of G T and an uncle (E T, 57) who had had attacks in his youth were interviewed and gave

various data. The onset of the disease in members of the family occurred consistently in the teens, attacks were usually nocturnal and generalized in character but exhibited what appeared to be a progressive nature. First the fingers, then the arms, legs and back were affected. Large meals were productive of attacks. R. T., 19, a brother of G. T., was reported to have had the most severe attacks, accompanied frequently with respiratory distress. He was extremely obese. The familial trait, according to the statement of E. T., had affected every sibling of E. T. and the father of the young men interviewed but could not be traced farther back.

COMMENT

The existence of two families afflicted with periodic paralysis, living within 10 miles of each other and apparently unrelated, leads to the speculation that the disease is more common than is generally believed. The hypothesis is strengthened by the observation that in the two families on whom data are reported, the trait had skipped no generation, and that in family A, it had affected a large percentage of those members of the two adult generations on whom information was available. Many of the persons were affected by attacks differing radically from the classic flaccid quadriplegia with which periodic paralysis is usually associated. In some cases, the only indication of the disease was a slight recurrent weakness of one limb. If a patient were to be seen with such a flaccid paresis of one or both arms or legs, of sudden onset, and if no family history were available (approximately 20 per cent of the cases hitherto reported were apparently nonfamilial), the correct diagnosis might well be obscure. It is to be noted that in family A, as in most of those previously reported, the disease affected males more commonly and more severely than females.

That the paralysis of this syndrome bears some relation to the metabolism of potassium seems to have been established since 1937 and 1938, when it was noted that there was a pronounced drop in serum potassium coincident with attacks, and that administration of potassium chloride shortened attacks. All patients in the present series observed that even the small doses which they had been taking shortened the duration of the paralysis. Recently, discussion has centered around the question of exactly how the fall in serum potassium is related to the attacks. Aitken and his co-workers^{7a} noted a direct correlation between the depth of paralysis and the level of serum potassium, their opinion, supported recently by Danowski, Elkington and Winkler,⁸ who carefully studied the course of the potassium ion during and after an attack, was that the diminished level of potassium in extracellular fluid, with its resultant effect on neuromuscular mechanism, was the probable causative element in the paralysis.

There is much evidence, admitted by the authors mentioned, which militates against such a theory. Most investigators have reported no correlation between the depth of paralysis in attacks and the level

of serum potassium Numerous cases have been reported in which the level of potassium was such as caused no paralysis in normal persons,¹² and some cases have been reported in which the level of serum potassium remained in the normal range throughout the attack.¹³ To these data may be added those in the case of A L, in which two attacks were accompanied by a serum potassium level considered normal Conversely, normal persons when given epinephrine U S P (adrenalin®), dextrose or insulin often show, with no clinical signs, a fall in serum potassium to levels that produce paralysis in patients with the disease.¹⁴ Lastly, the sudden elevation of serum potassium by the rapid intravenous administration of 1 Gm of potassium chloride during a paralytic attack had no noticeable effect on A L, confirming the data obtained by Hildebrand and Kepler.¹⁵

It appears more likely that the basic defect in the disease is a disorder of the contractile mechanism of muscle itself, possibly based on chronic deficit of potassium Zabriskie and Frantz¹⁰ demonstrated that their patient displayed persisting weakness only in the muscles of the forearm after immersion of the arm in cold water Using the same procedure and comparing the result with controls, I confirmed their finding The patient showed definite weakness a half hour after recovery of the controls.¹⁶ It is difficult to conceive that a generalized humoral abnormality, of itself, could yield such a local response to a local stimulus One other observation relevant to the question of muscular abnormality in this disease is that during an attack the paralyzed muscles do not have the limp, flabby consistency of denervated muscle It was noted by me, and independently by other observers, that the affected muscles had a firm and rubbery feel on palpation, which disappeared on recovery Pathologic studies of muscles during attacks have yielded no consistent results, and no explanation is offered for the finding except that it may indicate a local disorder of soft tissue It may have some relation to the frequent observation by

12 Talbott³ Ferrebee, Atchley and Loeb^{7d}

13 Watson, C W Familial Periodic Paralysis Report of a Case Showing No Changes in Serum Potassium Level with Description of Electroencephalographic Findings, *Yale J Biol & Med* **19** 127 (Oct) 1946

14 (a) Castleden, L I M The Effect of Adrenalin on the Serum Potassium Level in Man, *Clin Sc* **3** 241 (April) 1938 (b) Allott, E N, and McArdle, B Further Observations on Familial Periodic Paralysis, *ibid* **3** 229 (April) 1938

15 Hildebrand, A G, and Kepler, E J Familial Periodic Paralysis Associated with Exophthalmic Goiter, *J Nerv & Ment Dis* **94** 713 (Dec) 1941

16 An unaffected member of each of the two families reported here was tested similarly, with normal results Such testing of normal members of afflicted families might yield informative results as to the transmission of this muscular abnormality

patients that by exercising their muscles they were able to abort an incipient attack, whereas rest led to further weakness

There is evidence that the disease bears some relation to carbohydrate metabolism. Many patients, such as those in the present study, discovered that "heavy meals" preceded attacks, and Shinosaki^{6b} demonstrated that attacks could be produced by the administration of sugar. In the case of A. L., administration of 200 Gm of dextrose failed only once to produce an attack. The paralysis, however, has apparently no relation to blood sugar itself, Talbott⁸ pointed out that numerous investigators have found no consistently abnormal results in tests of blood sugar or dextrose tolerance during attacks. It is more probable that the pathologic process occurs in the mobilization of glycogen. Evidence of this supposition was the curious observation in the present study, confirming many other reports, that a period of several hours (eight or ten in the present case) intervened between the administration of the carbohydrate and the onset of the paralysis. The interval persisted whether the carbohydrate was administered in the morning or at night, but it appeared that the interval prior to the attack must be accompanied by rest, sleep was not essential. Apparently the ingestion of dextrose may have effects which are latent for several hours, this was suggested by the onset in the case of A. L. of mild weakness eight hours after the stimulus, disappearance of the weakness with physical activity, and its pronounced reappearance after a night's sleep. It is also suggestive with reference to carbohydrate metabolism that 3 of the patients whose cases are reported (cases 4, 7 and 10) showed a coincidence of obesity and particularly frequent and severe attacks, suggesting a parallelism to diabetes mellitus.

There has been some speculation as to the relation of the presumptive abnormal glycogen metabolism to the known abnormal potassium metabolism. It was definitely determined that the potassium which disappears from the blood is not excreted,¹⁷ and it was presumed that it entered the intracellular fluid. Danowski and others⁸ have recently demonstrated that this actually takes place by the finding, after ingestion of carbohydrate by their patient, first of a small negative potassium balance, with the potassium leaving the intracellular fluid, and then of a pronounced migration of potassium from serum to intracellular fluid, accompanied with a fall in serum potassium and the onset of paralysis. Administration of potassium chloride first caused a rise in intracellular potassium and then a rise in extracellular potassium, accompanied with recovery. The authors stated the prob-

¹⁷ Pudenz, McIntosh and McEachern^{7b} Gammon, Austin, Blithe and Reid^{7c} Allott and McArdle^{14b}

ability that the tissue into which the potassium entered was muscle, and while they stated the belief that the paralysis was due to the low potassium level of extracellular potassium, they pointed out that their results could also indicate a "chronic deficit" of muscle potassium. Gass, Cheikasky and Savitsky⁹ recently speculated on the possible nature of this "potassium deficit." Confirming the discovery of previous investigators¹⁸ that a disturbance of phosphorus metabolism parallels that of potassium, they expanded the hypothesis, mentioned by the earlier authors, that the basic disorder of the disease involves the hexosephosphate phase of carbohydrate metabolism. Pointing out that for two biologic processes—deposition of glycogen in liver muscle, and resynthesis of energy-rich compounds necessary for muscular contraction—potassium has been shown to be essential, Gass and his associates hypothesized that there is insufficient potassium in these patients to meet the double demand, particularly when additional carbohydrate is administered, thus the contractile mechanism suffers, and paralysis results.

SUMMARY AND CONCLUSIONS

Two families with periodic paralysis are described, case reports of 10 patients are presented. The great variability of signs and symptoms shown in the disease and the mild, atypical nature of many manifestations are stressed.

1 Attacks were produced regularly in 1 case by administration of 200 Gm of dextrose by mouth. Insulin, on one occasion, and water diuresis, on two occasions, failed to produce attacks.

2 Paralysis in the patient in this case ensued never less than eight hours, and on one occasion twenty-four hours, after ingestion of dextrose. Rest after ingestion of dextrose appeared essential for precipitation of an attack.

3 Serum potassium values during paralysis were low normal on two occasions and pathologically low on two others. Oral administration of potassium chloride appeared to hasten the return of muscular power. Intravenous administration of potassium chloride was ineffective on one occasion.

4 After exposure to cold for one-half hour, forearm muscles of the patient studied showed weakness for one-half hour, compared to ten minutes' weakness in controls.

The relation of these data to the pathogenesis of the disease is discussed.

¹⁸ Ferrebee, Atchley and Loeb^{7d} Allott and McArdle^{14b} Milhorat, A. T. The Metabolism of Phosphorus in Periodic Family Paralysis, *J. Clin. Investigation* **16** 676 (July) 1937.

CLINICAL SYNDROME OF OCCLUSION OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY

Report of Three Cases

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THE SYNDROME of occlusion of the posterior inferior cerebellar artery was first firmly established by Wallenberg¹ in 1895. Prior to that time, there had been several reports strongly suggestive of this syndrome.² In Wallenberg's studies of the anatomic distribution and variations of the posterior inferior cerebellar artery, he noted that the vessel was often absent on the right side. He stated that a portion of the lateral medullary region is completely devoid of blood supply when the artery is occluded, although a part is supplied by the collateral circulation. The bloodless area includes the restiform body, the direct spinocerebellar tract, the descending root of the trigeminal nerve, the motor nucleus of the vagus nerve (the nucleus ambiguus), a portion of the hypoglossal nucleus and a portion of the cerebellum. With this information, one may predict the clinical features of the syndrome.

The onset is usually sudden, without loss of consciousness. The patient experiences dizziness and headache and falls toward the side where the lesion is located. He notices inability to swallow and numbness or paresthesia of the contralateral side of the body and the homolateral side of the face. Objectively, diminution or loss of pain and temperature sensibility may be noted along the distribution of the trigeminal nerve on the side of the lesion and on the contralateral side of the body below the head. The sense of touch is, as a rule, not involved. Ataxia of the homolateral extremities is present. There is homolateral paralysis of the soft palate and the muscles of deglutition,

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1 Wallenberg, A. Acute Bulbaraffection (Embolie der Arterie cerebellar posterior inferior sinistra?), *Arch f Psychiat* **27** 504, 1895.

2 Senator, H. Apoplektische Bulbarparalyse mit wechselständiger empfindungslähmung, *Arch f Psychiat* **11** 713, 1881. Reinhold, H. Beiträge zur Pathologie der acuten Erweichungen des Pons und der Oblongata, *Deutsche Ztschr f Nerven* **5** 351, 1894. Eisenlohr, C. Ueber acute Bulbar- und Ponsaffektionen, *Arch f Psychiat* **9** 1, 1879.

which results in complete inability to swallow and in deviation of the uvula away from the side of the lesion. There is often a sympathetic disturbance, causing homolateral Horner's syndrome, with miosis, enophthalmos, ptosis of the lid and decreased perspiration. Nystagmus and homolateral facial paresis may also be present, due to involvement of Deiters' nucleus and the nucleus facialis, respectively.

This is the classic picture, depending on variations in the distribution of the vessel, some of these symptoms may be absent, and others may be present. The paralysis of the muscles of deglutition, the ataxia and the sensory changes, however, are almost invariably present.

In 1902, Breuer and Marburg³ showed experimentally that occlusion of the posterior inferior cerebellar artery cannot readily be distinguished from occlusion of the vertebral artery. It is generally thought, however, that occlusion of the latter vessel leads to pyramidal tract signs which are not present when the former vessel alone is involved.⁴ Of course, a thrombus in the posterior inferior cerebellar artery may propagate and occlude the vertebral artery itself, thereby involving other areas of the medulla and confusing the clinical picture.

Hun⁵ and Spiller^{4a} were the first to report cases with autopsy studies in the United States. Since their time, there have been sporadic reports. In 1930, Merritt and Finland⁶ presented reports of 6 cases recorded at the Boston City Hospital within a two year period. In the same year, Riley^{4b} reported 8 cases, also within a two year period, at Battle Creek, Mich.

In 1929, Freidowitsch⁷ reported a case in a patient with syphilitic aortitis. The patient improved with specific antisyphilitic therapy, and

3 Breuer, R., and Marburg, O. Zur Klinik und Pathologie der apoplektiformen Bulbarparalyse, *Arch u d neurol Inst u d Wien Univ* **9** 181, 1902

4 (a) Spiller, W. G. The Symptom-Complex of Occlusion of the Posterior Inferior Cerebellar Artery. Two Cases with Necropsy, *J Nerv & Ment Dis* **35** 365, 1908. (b) Riley, W. H. The Syndrome of Occlusion of the Posterior Inferior Cerebellar Artery, *Bull Battle Creek Sanitar & Hosp Clin* **25** 1, 1930. (c) Thompson, R. H. Occlusion of the Posterior Inferior Cerebellar Artery. Clinical Study of Four Cases, *Arch Neurol & Psychiat* **22** 530 (Sept) 1929. (d) Gordinier, H. C. Occlusion of the Posterior Inferior Cerebellar Artery, a Definite Symptom Complex, *Albany M Ann* **32** 585, 1911. (e) Holmes, W. H. Occlusion of the Postero-Inferior Cerebellar Artery, *M Clin North America* **9** 1544, 1926.

5 Hun, H. Analgesia, Thermic Anaesthesia, and Ataxia Resulting from Foci of Softening in the Medulla Oblongata and Cerebellum Due to Occlusion of the Left Inferior Posterior Cerebellar Artery, *New York M J* **65** 513, 581 and 613, 1897.

6 Merritt, H., and Finland, M. Vascular Lesions of the Hind Brain (Lateral Medullary Syndrome), *Brain* **53** 290, 1930.

7 Freidowitsch, G. N. The Symptomatology of Thrombus of Arteria Cerebelli Posterior Inferior, *Sovrem psikhonevrol* **8** 355, 1929.

it was presumed that syphilis was the etiologic basis for the occlusion. In 1942, Bianchi, Iribarren and Querol⁸ reported a case in which postmortem examination revealed syphilitic arteritis of the left vertebral artery, with thrombosis of the posterior inferior cerebellar branch. Despite these and other reports⁹ which stress the importance of syphilis as an etiologic basis, there is no doubt that atherosclerosis is, by far, the commonest underlying factor.

Although the syndrome is commoner than was previously believed, instances in general hospitals are still relatively rare, and internists in general are not well acquainted with the symptom complex. It is felt, therefore, that the 3 cases of the syndrome of the posterior inferior cerebellar artery recorded at Beth Israel Hospital within the past year are worth reporting and that a brief review of the symptom complex is timely.

REPORT OF CASES

CASE 1—A R., a white woman of 71, suddenly became dizzy and vomited twenty-four hours before admission to the hospital. On attempting to walk, she experienced severe vertigo and staggered to the right. There was no loss of consciousness. Several hours later, the patient complained of inability to swallow and of continuous pain in the left scapula. The past history, except for hypertension of many years' duration, was noncontributory.

Physical Examination—The patient was a well developed, fairly well nourished elderly white woman, dehydrated and cyanotic. She was slightly dyspneic. There was an audible gurgling from the throat, and, at frequent intervals, paroxysms of coughing occurred. The patient was unable to swallow. Frequent suction of the posterior part of the pharynx was necessary to prevent recurrent cough and cyanosis. The blood pressure was 190 systolic and 90 diastolic, the pulse rate was 96 beats per minute, the temperature was 99.6 F, and there were 20 respirations per minute. Funduscopic examination could not be satisfactorily performed. The heart was slightly enlarged, and a soft blowing apical systolic murmur was audible. A few medium inspiratory rales were present at the base of both lungs. The abdomen was distended and tympanic.

Neurologic Examination—The tongue was in the midline. The gag reflex was absent. Slight ptosis of the right eyelid was present. The pupils were miotic, round and equal in size. They reacted well to light and in accommodation. The function of deglutition was absent. The right side of the face and the left half of the body were anesthetic to pain sensibility. Because of poor cooperation, the sensibility to touch and temperature could not be tested. Ataxia of the right arm and leg was demonstrable, and questionable slight weakness of the same extremities was present.

8 Bianchi, A., Iribarren, L., and Querol, H. E. Goma intracerebeloso y síndrome de la arteria cerebelosa postero-inferior (síndrome de Wallenberg), *Rev Asoc med argent* 56:183, 1942.

9 Kozhevnikov, A. M. Thrombosis of the Posterior Inferior Cerebellar Artery, *Russk Klin* 8:45, 1927. Wilson, G., and Winkelman, N. W. Occlusion of the Posterior Inferior Cerebellar Artery, *J Nerv & Ment Dis* 65:125, 1927.

Course—Because of the cyanosis and the basal rales, the patient was placed in an oxygen tent, digitalized and given a mercurial diuretic. Twenty-four hours after admission, the temperature rose to 102 F, and penicillin therapy was instituted. A diagnosis of aspiration pneumonia was made and confirmed roentgenologically.

The patient could take nothing by mouth, all attempts to feed her in that manner resulted in aspiration, cough and cyanosis. Nutrition was maintained with a Levin tube for three weeks. Thereafter, deglutition gradually returned, and the patient was able to swallow soft foods. There was little change in the sensory dysfunction or the ataxia. She was discharged and observed thereafter for one year. All signs and symptoms gradually improved until at the end of the observation period no residua remained.

CASE 2—H. R., a white man of 56, was awakened at 3 a. m., with dizziness, nausea, vomiting and difficulty in swallowing. In attempting to walk to the bathroom, he noted pronounced vertigo and a tendency to fall to the right. He complained also of numbness of the right side of the face. There was no loss of consciousness. One year previously, the patient had experienced precordial discomfort on exertion, and a diagnosis of arteriosclerotic heart disease with mild coronary insufficiency had been made.

Physical Examination—The patient was a well developed, well nourished white man. At the time of the examination, he was lying quietly in bed, with his eyes closed. The speech was slurred, and he complained of vertigo whenever he opened his eyes. The blood pressure was 190 systolic and 100 diastolic. No cardiac enlargement was demonstrated. A soft blowing apical systolic murmur was audible. The lungs were clear.

Neurologic Examination—There was mild paresis of the right side of the face, of central origin. The tongue and uvula deviated slightly to the left. There was inability to swallow, and attempts to drink water resulted in severe paroxysms of coughing. The right side of the face and the left half of the body, below the head, were anesthetic to pain and temperature sensibility. The sense of touch was preserved. There was dyssynergia of the right arm and leg and dysdiadochokinesis of the right arm. Horizontal nystagmus was demonstrable, particularly on lateral gaze to the right, with the rapid component toward the right.

Course—Forty-eight hours after admission, Horner's syndrome became noticeable on the right side. There were ptosis, enophthalmos and miosis, with a definite dryness of the skin over the right side of the face. For the first five days it was necessary to catheterize the patient, but thereafter urination was spontaneous. Singultus was an intermittent symptom for the first three weeks. For the first twenty-one days, nutrition was maintained with a Levin tube and intravenous infusions. After the third week, the patient was able to swallow thick, pureed foods. At the end of the fourth week, the function of deglutition had in part returned, but there were occasional aspiration and regurgitation through the nose, particularly of fluids. At that time, the ataxia of the right side of the body had lessened. There was no change in the sensory dysfunction. The nystagmus was still present, and sitting up quickly brought on considerable dizziness.

The patient gradually improved over a period of time, at the time of writing, eight months later, few residual neurologic signs can be elicited. There remain slight impairment of pain and temperature sensations on the left side of the body and a slight tendency to fall to the right while walking. Results of the remainder of the neurologic examination are negative.

One month before the time of writing, the patient underwent a two stage prostatectomy uneventfully

CASE 3—R B, a white woman of 57, experienced sudden onset of faintness, nausea and vomiting and inability to see clearly about six hours before admission to the hospital. There was no loss of consciousness. When seen in the emergency room, the patient complained of inability to swallow, slurred speech and numbness of the left half of the face. There was a past history of hypertension of sixteen years' duration. Fourteen years prior to admission, the patient had sustained a myocardial infarct, with no subsequent evidence of coronary insufficiency or of congestive failure. Seven months before the present episode, the patient had had a cerebrovascular accident, with transient right hemiparesis and left facial paresis. During the year previous to admission, there had been frequent episodes of dizziness and headache.

Physical Examination—The patient was well developed and well nourished. She had slurred speech and coughed sporadically. The blood pressure was 190 systolic and 130 diastolic. The fundi showed grade 2 arteriosclerosis. The heart

Pathoanatomic Changes and Neurologic Signs in 3 Cases

Areas of Involvement	Signs	Case 1	Case 2	Case 3
Nucleus ambiguus	Difficult deglutition	Yes	Yes	Yes
Sensory root of trigeminal nerve	Homolateral facial anesthesia	Yes	Yes	Yes
Internal medullary sympathetic center	Horner syndrome	No	Yes	Yes
Lateral spinothalamic tract	Contralateral anesthesia of body to pain and temperature sensibility	Yes	Yes	Yes
Direct spinocerebellar tract	Homolateral ataxia	Yes	Yes	Yes
Deltors' nucleus	Nystagmus, dizziness, falling to side of lesion	Yes	Yes	Yes
Nucleus facialis	Homolateral facial paresis	No	Yes	Yes

was moderately enlarged to the left, and a soft, blowing, grade 1 systolic murmur could be heard over the base. The lungs were normal.

Neurologic Examination—There was central facial paresis and Horner's syndrome on the left. Both pupils reacted to light and in accommodation. The left pupil was miotic. The gag reflex was absent, and the uvula deviated to the right. The function of deglutition was completely absent. Attempts at swallowing even a few drops of water resulted in aspiration, severe paroxysms of coughing and cyanosis. The tongue deviated to the right. There was horizontal nystagmus, particularly with lateral gaze to the left. Anesthesia to pain and temperature sensibility was demonstrable along the distribution of the left trigeminal nerve and over the right half of the body below the head. There was dyssynergia of the left arm and leg and dysidiadokokinesis of the left arm.

Course—For the first five weeks, feeding was accomplished with a Levin tube. Return of the function of deglutition was extremely slow, and it was not until after the twelfth week that the patient was able, with some difficulty, to swallow soft foods. At the end of the third month, there was some improvement in the ataxia, but results of the remainder of the neurologic examination was unchanged. The patient was then discharged. Further follow-up was not possible.

The table represents an outline of the pathoanatomic changes and the neurologic signs in the 3 cases.

COMMENT

The classic clinical picture of occlusion of the posterior inferior cerebellar artery is so striking that, once seen, it is unforgettable. On the basis of the neuroanatomy involved, one can visualize and explain practically the entire syndrome.

The posterior inferior cerebellar artery arises from the vertebral artery and supplies the lateral portion of the medulla and the adjacent portion of the cerebellum. The term "lateral medullary syndrome" which is sometimes applied to this symptom complex⁶ is therefore self explanatory. The nucleus ambiguus, or the motor nucleus of the vagus, which is in the involved area, is responsible for the paralysis of the muscles of deglutition. Since the fibers to the larynx and palate also originate in this nucleus, the deviation of the uvula and the frequently associated hoarseness are thus explained.

The dizziness, falling to the side of the lesion and nystagmus result from involvement of Deiters' nucleus (in the vestibular nucleus) and of its connecting nerve pathways to the ocular motor nuclei. The function of Deiters' nucleus is that of maintaining equilibrium, through various pathways in the brain and the spinal cord, it controls related movements of the head, eyes and body. These pathways do not cross prior to their emergence from the central nervous system and, therefore, give homolateral signs.

The Horner syndrome, also a homolateral sign, consists of miosis, enophthalmos, ptosis of the upper eyelid and diminution in perspiration on the face. These signs result from involvement of the sympathetic center in the lateral portion of the medulla. The facial paresis which is sometimes seen may also be related to the sympathetic center but is sometimes a result of involvement of the facial nerve or its nucleus.^{4b}

The sensory changes are dissociated. There are homolateral analgesia and thermanesthesia, whereas tactile sensibility is unimpaired. This phenomenon has been explained by Spiller,^{4a} Riley,^{4b} Gerard,¹⁰ Stopford¹¹ and others by the fact that the descending root of the trigeminal nerve, which carries the fibers for pain and temperature sensibility, is in the involved area. The pathways for tactile sensibility go to the main sensory nucleus of the fifth nerve, which is placed more anteriorly in the brain stem, thus being missed by the lesion. The lateral spinothalamic tract, which carries the contralateral fibers for pain and temperature sensibility from the trunk and extremities, also passes through the lateral medullary region. This accounts for the

¹⁰ Gerard, M. W. Afferent Impulses of the Trigeminal Nerve, *Arch Neurol & Psychiat* **9** 306 (March) 1923.

¹¹ Stopford, S. B. The Function of the Spinal Nucleus of the Trigeminal Nerve, *J Anat* **59** 120, 1924-1925.

contralateral analgesia and thermanesthesia below the head. Again, the tactile sensibility is not impaired, since the fibers for this function apparently proceed with the ventral spinothalamic tract, which passes through the brain stem in a more ventral position¹²

The homolateral ataxia results from the involvement of the direct spinocerebellar tracts or the restiform body, or both

The 3 cases described presented more or less classic pictures of occlusion of the posterior inferior cerebellar artery. In cases 1 and 2, the involved vessel was on the right, whereas in case 3 it was on the left. This distribution is a little unusual; Wallenberg¹ stated that the artery is often absent on the right side. In all our cases, the nucleus ambiguus, Deiters' nucleus, the sensory root of the trigeminal nerve, the lateral spinothalamic tract and the direct spinocerebellar tract were involved. The dysfunction of the nuclei and the pathways were manifested by inability to swallow, vertigo, nystagmus and falling to the side of the lesion, homolateral facial analgesia and thermanesthesia, contralateral analgesia and thermanesthesia below the head and homolateral ataxia. In addition, in cases 2 and 3, the lateral medullary center for the sympathetic nervous system and the nucleus facialis were involved, as manifested by homolateral Horner's syndrome and homolateral paresis of the face, of central origin. In none of these cases was there a sign of dysfunction referable to the pyramidal tract. On this basis, we believe that the vertebral artery per se was in no way affected. Finally, it is stressed that in these 3 cases there was no loss of consciousness. This phenomenon has been noted by various authors as characteristic of the lesion, in contradistinction to other forms of cerebrovascular accidents.

Etiologically, arteriosclerosis is the most important factor. Some authors, particularly Salmon¹³ and two other groups of workers,⁹ stressed syphilis as having a causal relationship. As mentioned previously, Bianchi, Iribarren and Querol⁸ reported a case of occlusion of the posterior inferior cerebellar artery in which postmortem examination revealed syphilitic arteritis of the left vertebral artery, with thrombosis of the posterior inferior cerebellar branch. Despite these isolated instances, a more recent report^{4b} stresses hypertension and arteriosclerosis as the commonest etiologic basis. In each of the 3 cases reported in the present study, there was evidence of hypertension and arteriosclerosis. The patient in case 1 had hypertension of long standing. In case 2, there was a history of hypertension and coronary insufficiency. The patient in case 3 had had hypertension for many

12 Best, C. H., and Taylor, N. B. *The Physiologic Basis of Medical Practice*, ed. 2, Baltimore, Williams & Wilkins Company, 1940.

13 Salmon, A. La trombosi delle arterie bulbari, *Riforma med.* 29:649, 1913.

years and had sustained both a myocardial infarct and a cerebrovascular accident in the past

Another factor to be considered is the manner in which the artery originates and branches ^{4b} The posterior inferior cerebellar artery arises at nearly a right angle to the vertebral artery, and the branches which penetrate the medulla do likewise This arrangement interferes with the free circulation of blood and may be a factor in the development of a thrombus in an already arteriosclerotic artery

A rather uncommon etiologic factor was reported by Davison and Spiegel ¹⁴ In their case, a metastatic neoplasm was the basis of the lateral medullary syndrome

In the differential diagnosis, one must consider occlusion of the vertebral artery, the anterior spinal artery and the artery of the lateral recess The absence of signs of involvement of the pyramidal tract excludes the possibility of involvement of the vertebral artery ^{4c} The anterior spinal artery is a branch of the vertebral artery and supplies the central and anterior portions of the medulla, including the pyramids ^{4a} It is, therefore, obvious that occlusion of that vessel would also lead to signs in the pyramidal tract, thus differentiating the lesion from that of the syndrome of the posterior inferior cerebellar artery The artery of the lateral recess supplies an extremely small, localized area in the medulla and in no way gives the classic picture of the Wallenberg syndrome ³

The immediate therapy is, of necessity, the maintenance of nutrition The patients cannot swallow, and it may be necessary to feed them parenterally or with a Levin tube for many weeks The gastric tube may be inserted with each feeding or left in situ for several days at a time Aspiration pneumonia is common, and antibiotic therapy may be necessary on occasion When the patient begins to swallow, it is best to give thick, pureed foods, since these are apparently not too easily aspirated

The use of antisyphilitic therapy in those cases in which syphilis is present is definitely indicated A dramatic response has been reported ⁷ in a case in which the basis was syphilitic arteritis Ordinarily, however, one should not expect too startling a result, since the damage to the medulla occurs before symptoms are noted

Anticoagulant therapy in this syndrome is a controversial issue, as it is in all cerebrovascular accidents The possibility of converting a thrombus to a hemorrhage is something to fear Magnusson, ¹⁵ how-

14 Davison, C, and Spiegel, L A Syndrome of Posterior Inferior Cerebellar Artery from Metastatic Neoplasm, *J Neuropath & Exper Neurol* 4 172, 1945

15 Magnusson, J H Thrombosis of the Posterior-Inferior Cerebellar Artery (Wallenberg Syndrome) Treated with Heparin, *Lancet* 1 666, 1938

ever, reported a remarkable result in a case in which heparin sodium was given

The prognosis with regard to life and the return of essential functions is generally good. The ataxia and inability to swallow often improve after several months. It must be remembered, however, that the syndrome is an indication of more generalized vascular disease, in which sudden death is no uncommon occurrence.

SUMMARY

Three cases of the syndrome of occlusion of the posterior inferior cerebellar artery are presented. The patients were seen in a general medical service in one hospital within a period of one year.

The syndrome as originally described by Wallenberg is still, for practical purposes, pathognomonic. The symptom complex usually includes sudden onset with no loss of consciousness, dizziness, falling toward the side of the lesion, nystagmus, difficult deglutition, homolateral Horner's syndrome, ataxia, trigeminal analgesia and thermesthesia and contralateral analgesia and thermesthesia of the body.

The basis for the symptom complex is a highly localized lateral medullary lesion, involving the nucleus ambiguus, Deiters' nucleus, the descending root of the fifth nerve, the lateral spinothalamic tract, the medullary sympathetic center, the direct spinocerebellar tract, the restiform body and, occasionally, the nucleus facialis.

The etiology, differential diagnosis, therapy, prognosis and course are briefly discussed.

RELATION OF PULMONARY EMBOLISM TO PERIPHERAL THROMBOSIS

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THE MOST dreaded complication of venous thrombosis is pulmonary embolism, for which the mortality rate is about 15 per cent¹. The need is for additional data which may be of help in understanding the thromboembolic phenomena and, thus, in reducing the danger. Accordingly, a necropsy study was made in the hope that it would yield information for further clinical and laboratory evaluation.

Knauer² reported that the incidence of fatal pulmonary embolism in a series of 33,558 autopsies was 2.5 per cent. Barnes³ estimated that 34,000 persons die of pulmonary embolism each year in this country. Hunter and his co-workers⁴ observed that 52.7 per cent of older people confined to bed evidenced thrombosis of the deep veins of the leg. In the necropsies reported by them, pulmonary embolism accounted for 3.13 per cent of all deaths, the authors concluded that the most important single cause of thrombosis of the leg veins in older persons was the sudden confinement to bed of previously ambulatory patients.

Read at the meeting of the New York Pathological Society, New York Academy of Medicine, Dec 20, 1948.

From the Third (New York University) Division, Goldwater Memorial Hospital, Welfare Island, and the Department of Medicine, New York University College of Medicine.

1 Cosgriff, S. W., in discussion on Thromboembolism, *Am J Med* **3** 753 (Dec) 1947.

2 Knauer, J. G. Acute Cor Pulmonale. Discussion of Literature and Report of Case Successfully Treated with Oxygen, *Bull Am Acad Tuberc Physicians* **3** 36, 1939, cited by Rubin, E. H. *Diseases of the Chest with Emphasis on X-Ray Diagnosis*, Philadelphia, W. B. Saunders Company, 1947.

3 Barnes, A. R. The Problem of Pulmonary Embolism, *West J Surg* **50** 551 (Nov) 1942.

4 Hunter, W. C., Sneed, V. D., Robertson, T. D., and Snyder, G. A. C. Thrombosis of the Deep Veins of the Legs, *Arch Int Med* **68** 1 (July) 1941.

The present study was made at Goldwater Memorial Hospital, an institution devoted to the study of chronic diseases. The vast majority of patients were in the older age groups and had been confined to bed from time to time. In order to determine the frequency of thrombosis and embolism in this hospital, as well as the relation of both conditions to the final autopsy diagnosis, the present study was undertaken.

MATERIAL

Analysis was first made of 202 consecutive routine autopsies performed at the hospital. The group consisted of 67 female and 135 male persons, the ages ranging from 18 to 89 years. Only 20 patients were below the age of 50, and of these one half were younger than 40. As is evident in the analysis of the material, the diagnosis of cirrhosis of the liver assumed a singular role, for this

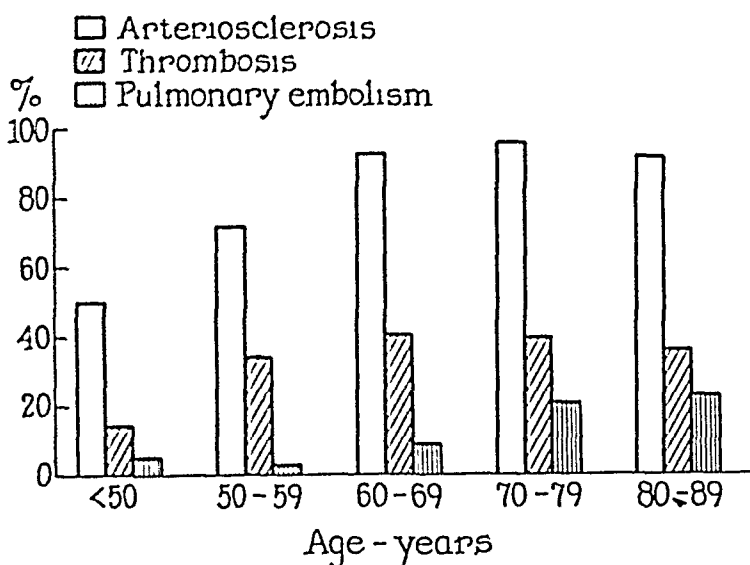


Chart 1—Incidence of three conditions according to age

reason, protocols of an additional 79 consecutive autopsies in which there had been a final diagnosis of Laennec's (portal) cirrhosis were selected for further analysis. Besides these, 217 protocols of autopsies performed on the bodies of patients of selected age groups without cirrhosis were reviewed, giving a total of 516 cases.

ANALYSIS OF THE DATA

Chart 1 shows the incidence of arteriosclerosis, thrombosis and pulmonary embolism in patients of several age groups. The number of cases of arteriosclerosis includes only those in which the protocol of the autopsy described the process as moderate or pronounced. The number of cases of thrombosis includes those in which there were autopsy findings of peripheral as well as cardiac thrombi. Since these were routine autopsy reports, detailed descriptions of dissection of the peripheral veins were not included. Consequently, no conclusions about the absolute incidence of peripheral thrombosis were justified. However, since all autopsies were performed by a similar routine, a comparison of incidence in persons of different ages and with different types of disease may be valid. The problem

of inaccuracy was not evident in considering the incidence of pulmonary embolism, since in all necropsies the pulmonary vessels were routinely dissected to their small ramifications

From chart 1 it is evident that the incidence of arteriosclerosis was so high that it was difficult to correlate other findings with it. It may also be noted that the incidence of thrombosis was greater in the age groups beyond 50 than in the younger persons. However, when the group of persons over 50 was broken down by decades no significant difference in the incidence of thrombosis was apparent.

The frequency of pulmonary embolism did not run parallel to the incidence of thrombosis. It was not until about the age of 70 that a sharp rise occurred in the incidence of pulmonary embolism. Incidentally, the frequency of pulmonary embolism in the group of persons under 60 was of the same order of magnitude as that reported by Knauer², however, after 70 the incidence of pulmonary embolism was much higher in the present series. Statistical treatment by the chi-square method

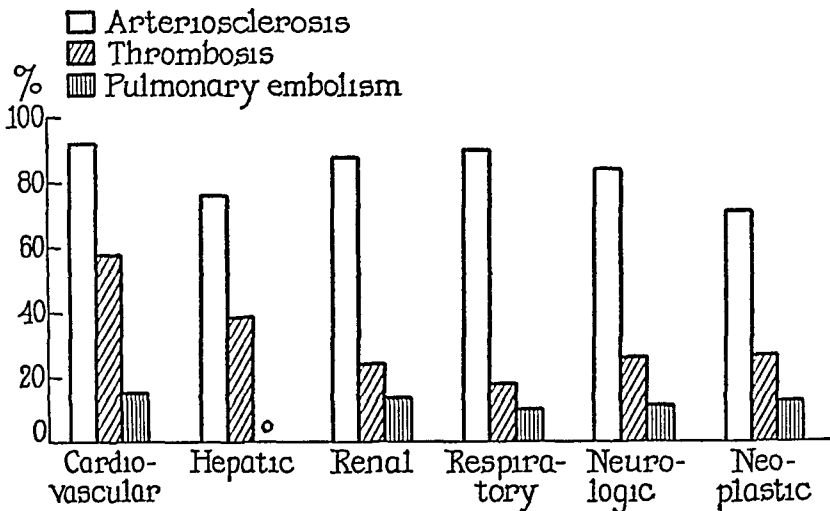


Chart 2—Incidence of three conditions according to type of disease present

showed a highly significant difference in the incidence of pulmonary embolism in the age group above 70 as compared to those groups below 70. The same two groups, however, demonstrated no significant difference in the incidence of thrombosis.

Chart 2 represents an effort to correlate the data concerning thromboembolism with the pathologists' final diagnosis. The final diagnosis was classified according to six major types of disease: cardiovascular, hepatic, renal, respiratory, neurologic and neoplastic. Those protocols which revealed major disease in more than one group were entered accordingly. The group of patients with hepatic disease included those with cirrhosis of the Laennec type but did not include those with so-called cardiac cirrhosis. From the nature of the tabulation, it was to be expected that the group of patients with cardiovascular disease would show by far the greatest incidence of thrombosis. It is interesting that thrombosis was not less frequent in the group of patients with cirrhosis than in the remaining four groups and was of about equal frequency in the four groups. By contrast, the incidence of pulmonary embolism ranged from 10 to 15 per cent in all groups with the one startling exception of that composed of patients with hepatic cir-

rhosis In 97 cases in which the postmortem diagnosis was Laennec's cirrhosis there were no pulmonary emboli The same group of patients, with the possible exception of 1, also had no peripheral emboli In no other group analyzed were emboli so noticeably lacking

Statistical analysis by the chi-square method revealed a probability of less than 1 in 1,000 that the result was due to chance Since the average age of the patients with portal cirrhosis was 62.8 and that of the patients without cirrhosis 68.0, the data were rearranged into equivalent age groups and again statistically analyzed, the results again demonstrated that the figures were significant

COMMENT

The data demonstrated a lack of pulmonary embolism in patients with Laennec's cirrhosis In the same patients, the incidence of cardiac and peripheral venous thrombosis was not particularly low It has been adequately established that the coagulation mechanism is apt to be disturbed in chronic disease of the liver However, the extent of hypocoagulability of the blood in such patients is not great In considering the relation of disturbed coagulation to the development of thrombosis and to embolization, it is especially noteworthy that the incidence of the two phenomena is not parallel Apropos of this fact, it is interesting that in certain cases of the migratory type of thrombophlebitis emboli seem never to be present We have seen examples of this disorder with venous thrombi extending over all four limbs and the chest wall, in which the disease continued unabated for months but no pulmonary emboli appeared during the period of illness On the other hand, as is well known, there are cases of migrating thrombophlebitis, clinically and pathologically indistinguishable from the previous variety, in which emboli to the lung are freely produced Apparently the factors which determine the development of venous thrombosis are not necessarily responsible for the liberation of pulmonary emboli

The foregoing analysis reveals further that a striking increase in thromboembolic disease exists only in the extremely advanced age groups, in which the patients are much older than the general average in ordinary hospital populations With Unger, two of us (M. W. and S. S.) have reported elsewhere⁵ that this same age group (over 70) has a high incidence of impaired liver function without clinical or morphologic evidence of hepatic disease

The reason for the greater frequency of pulmonary thromboembolism in the advanced age groups does not find adequate explanation in the combination of intimal alteration, reduction in the diameter of vascular lumens and slowing of the blood stream The magnitude of these changes is not remarkably greater in the eighth decade than

⁵ Unger, P., Wiener, M., and Shapiro, S. Vitamin K Tolerance Test, *Am J Clin Path* 18: 835 (Nov) 1948

in the preceding ten years. Contrary to the general impression, the coagulability of the blood in the more advanced years is demonstrably reduced as compared with the normal standard for all adults.

The mechanism of intravascular thrombus formation involves the interplay of a number of factors such as the rate of blood flow, the state of the surrounding wall of the vessel, the coagulability of the blood and possibly other factors, at present unknown. These factors seem to be interdependent, although the roles played by them are probably not of equal importance. Thus, the capacity of the blood to clot appears to be the major requirement for thrombus formation. Regardless of the extent of participation of the other factors, the formation of an intravascular clot may be inhibited or entirely prevented if the blood is rendered sufficiently hypocoagulable. It is likely that hypocoagulability of the blood is also of considerable importance in determining whether or not embolism will occur. However, there is good reason to suspect that other mechanisms are involved. In cirrhosis of the liver, fibrinolysis is extraordinarily active.⁶ This may be a factor in the rarity of pulmonary embolism in this disease. Incidentally, there is no conclusive proof that the efficacy of the anticoagulant drugs in preventing embolization is the result of the induced hypocoagulability per se. What is known of the conditions which are responsible for the formation of intravascular thrombi is inadequate to explain the variations in incidence of pulmonary embolism, as revealed in the data presented in this paper.

SUMMARY

An analysis is made of the incidence of thromboembolism, according to postmortem diagnosis, in patients in a variety of age groups and with various types of diseases. The following facts are noted:

In 278 miscellaneous cases, excluding those of Laennec's cirrhosis, the incidence of pulmonary embolism was 12 per cent (33 cases).

In 97 instances of Laennec's cirrhosis, the incidence of pulmonary embolism was 0. The incidence of cardiac and peripheral thrombosis in these cases of hepatic disease was not significantly different from that in the cases of miscellaneous diseases.

In the group of patients over 70, the incidence of pulmonary embolism was 21 per cent. In those from 50 to 70, it was less than 7 per cent. There was no similar variation in the incidence of thrombosis.

The dissociation of the incidence of pulmonary embolism and that of peripheral thrombosis is discussed.

⁶ Goodpasture, E. W. Fibrinolysis in Hepatic Insufficiency, *Johns Hopkins Hosp. Bull.* **25** 330 (Nov.) 1914.

PERNICIOUS ANEMIA IN EARLY ADOLESCENCE

Report of a Case in a Girl of Fourteen

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AND

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PERNICIOUS anemia is a disease of late adult life, rarely being encountered in patients under 30, and is exceedingly infrequent in children. Doubt has been expressed in many texts and articles as to whether true pernicious anemia ever occurs in infancy or childhood. A pernicious anemia-like disease, i. e., a macrocytic anemia with megaloblastic arrest of the bone marrow, may occur with *Diphyllobothrium* infection, syphilis, various gastrointestinal lesions, steatorrhea, or other conditions in which there is improper absorption or production of the maturation factor.¹ The commonest cause of macrocytic anemia in childhood is probably a diet deficient in the extrinsic factor. There have been many reports of pernicious anemia occurring in children, but the diagnosis was open to question in most cases, and Wintrobe^{1b} accepted only 2 cases with certainty. Peterson and Dunn,² in 1946, reviewed the literature on the subject, they accepted only 2 cases³ as proved but added 1 of their own. The familial tendencies of pernicious anemia are well recognized, and it is also recognized that the achlorhydria which is so prominent and frequent in families with pernicious anemia may occur at an early age in children whose parents have pernicious anemia.⁴

The present case apparently fulfils unequivocally the diagnostic criteria for pernicious anemia.

From the Department of Internal Medicine, State University of Iowa College of Medicine.

1 (a) Davis, L. J. Macrocytic Anemia in Children, *Arch. Dis. Childhood* **19** 147, 1944. (b) Wintrobe, M. M. *Clinical Hematology*, ed. 2, Philadelphia, Lea & Febiger, 1946.

2 Peterson, J. C., and Dunn, C. S. Pernicious Anemia in Childhood, *Am. J. Dis. Child.* **71** 252 (March) 1946.

3 Pohl, C. Über perniziöse Anämie im Kindesalter, *Monatsschr. f. Kinderh.* **84** 192, 1940. Dedichen, I. Anémie à type pernicleux chez un enfant de 9 mois, *Acta med. Scandinav.* **111** 90, 1942.

4 Wilkinson, J. F., and Brockbank, W. The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anemia, *Quart. J. Med.* **24** 219, 1931.

REPORT OF CASE

L. L., a girl of 14, had been well until December 1945, when an illness developed which was thought to be "flu." After two weeks of the illness, it was noted that the patient was jaundiced, the local physician made a diagnosis of severe anemia, for which she was given "liver pills." The fatigability persisted, the appetite remained poor, fever and swelling of the cervical lymph nodes developed and the patient was admitted to the University Hospitals in March 1946. There was no history of bleeding from any source, and the past history was noncontributory. The nutritional and dietary histories were normal until the onset of the present illness, and although the patient had acute cervical adenitis on admission, there was no history or evidence of a chronic infection.

The patient's mother had pernicious anemia and had been under treatment in the same hospital. It was reported, but not verified, that an aunt of the patient had pernicious anemia, and that a great-aunt had anemia of an unknown type.

Examination revealed a poorly nourished and chronically ill girl, with pronounced pallor and jaundice. The mucosa at the edges of the tongue was atrophic. The submaxillary lymph nodes were enlarged and tender, and there was chronic faucial tonsillitis. There was no other significant lymphadenopathy. The spleen was firm, nontender and easily palpable. The liver was not enlarged. The neurologic examination revealed normal reflexes and sensations in all areas. The remainder of the physical examination was noncontributory.

At the time of admission, there were 1,500,000 erythrocytes per cubic millimeter and 64 Gm of hemoglobin per hundred cubic centimeters, and a hematocrit reading of 16 per cent. The leukocyte count was 3,800 cells per cubic millimeter, with a differential count of 47 per cent neutrophils, 38 per cent lymphocytes and 15 per cent monocytes. The color index was 1.47 and the volume index 1.22, mean corpuscular hemoglobin was 42.6 micromicrograms and mean corpuscular volume 106 cubic microns. There was considerable variation in the size and shape of the erythrocytes on the blood smear, the predominant type of cell was large and deep staining. There were 90,000 platelets per cubic millimeter, 22 per cent of the erythrocytes were reticulocytes. Hemolysis of the erythrocytes began at 0.46 per cent sodium chloride solution and was complete at 0.26 per cent. Clot retractility was normal and prothrombin time was normal. The indirect van den Bergh test showed 51 mg of bilirubin per hundred cubic centimeters. The total amount of plasma protein was 7.5 Gm per hundred cubic centimeters, with 5.2 Gm of albumin, 2.2 Gm of globulin and 0.3 Gm of fibrinogen. Results of roentgenologic examinations of the esophagus, the stomach and the small and large intestine were entirely normal, and the examination of the feces for ova and parasites was negative. There was no bleeding from the gastrointestinal tract.

There was no free hydrochloric acid in the gastric content after stimulation with histamine.

The patient was given parenteral liver therapy, 15 units of liver extract were given daily for three days and then 15 units, twice a week. The reticulocyte count rose from 22 per cent to 26 per cent on the fifth day of treatment and dropped to 0.8 per cent on the twenty-second day. After thirty-six days of treatment, the patient was discharged from the hospital, at which time the erythrocyte count was 3,700,000 and the hemoglobin content, 7.3 Gm. Treatment was continued at home, and the girl was seen in the outpatient clinic from time to time. In September 1946, there were 10 Gm of hemoglobin, 5,000,000 erythrocytes and

12,000 leukocytes. Satisfactory hemoglobin and erythrocyte levels were maintained, but therapy became less regular, and in March 1947, 20 mg of folic acid (pteroylglutamic acid) per day was given orally in place of the parenteral administration of liver extract. Hemoglobin content and erythrocyte count were maintained at normal levels with this treatment through July 1947.

The patient then discontinued all treatment, in December of that year, she became tired and weak, and "flu" again developed. She was admitted to the hospital. Blood values were 1,900,000 erythrocytes, 7.2 Gm of hemoglobin, 6,700 leukocytes and 98,000 platelets. There was no evidence or history of bleeding from any point, and the fragility of the erythrocytes was normal. Bone marrow aspirated from the sternum showed megaloblastic hyperplasia characteristic of pernicious anemia.

Daily injections of 15 units of liver extract were given, and the reticulocytes count increased from 5 per cent to 24 per cent on the ninth day of treatment. The hemoglobin content and erythrocyte count returned to their normal values, the bone marrow reverted to normal and the patient improved clinically. In September 1948, the hemoglobin content was 12 Gm, the erythrocyte count, 4,600,000, and the leukocyte count, 8,150, and the patient was in excellent health. Secondary sex characteristics which had previously been underdeveloped, had now developed to normal for a girl of 17. The blood levels have been maintained at normal to the time of this report, with no return of jaundice or of the subjective manifestations.

L. L., the mother of the patient, was first admitted to the University Hospitals March 27, 1942, at the age of 50. She complained of tingling of the hands and feet, fear of falling and difficulty in threading a needle. Numbness had first appeared in the feet about a year previously, followed with stiffness of the legs, numbness and tingling of the hands, and such extensive progression of these symptoms that a fear of falling developed. The patient also had one episode of soreness of the mouth and tongue. She had received one course of injections of liver extract, of unknown amount.

Examination revealed the patient to have a spastic, ataxic gait. There were ataxia of both hands and feet, spasticity of the muscles, hyperactive tendon reflexes, bilateral Babinski reflexes and sustained ankle clonus, and diminution of pallesthesia, two point discrimination and sense of position. The Wassermann reactions of the blood and the spinal fluid were negative.

The blood showed 14 Gm of hemoglobin, 4,000,000 erythrocytes and 11,200 leukocytes, with a normal differential count. There was no free hydrochloric acid after stimulation with histamine. A diagnosis was made of subacute combined degeneration of the spinal cord, with pernicious anemia.

The patient was treated with intramuscular injections of liver extract, which resulted in subjective improvement but in little change in the objective evidence of the degeneration of the cord. She was last seen Aug. 24, 1948, at which time the blood count and hemoglobin content were at normal levels. There was achlorhydria, and there had been no progression of involvement of the spinal cord. The patient continues to take liver extract at the time of writing, she has a normal hematologic picture and no further progression of the neurologic complications.

COMMENT

The diagnosis of pernicious anemia in the girl of 14 seems to fulfil the most rigid requirements. The anemia was macrocytic and hyperchromic in type, with increased mean corpuscular volume and mean

corpuscular hemoglobin. It was associated with megaloblastic bone marrow. The leukocytes and platelets were both reduced in number. The appearance of the blood smear was typical of that in pernicious anemia in all respects. There were hyperbilirubinemia and persistent achlorhydria, which did not respond to injections of histamine.

Complete remission, with a reticulocyte crisis, was produced by the administration of a potent liver extract, and the blood was maintained at normal levels with liver extract and folic acid. The remission was characterized by a return of both peripheral blood and bone marrow values to normal. A relapse occurred when therapy was discontinued, and subsequent liver therapy produced another sustained remission. The presence of coexisting disease or dietary inadequacies which might produce anemia of this type could not be determined.

The mother of the patient was found to have combined sclerosis of the spinal cord and achlorhydria, she responded subjectively to the administration of liver extract and has been without relapse or progression of the disease while being given liver therapy.

SUMMARY

A case of pernicious anemia in a girl of 14 is presented, in which both liver extract and folic acid (pteroylglutamic acid) maintained the disease in complete remission.

ADDENDUM

Since completion of this paper, a gastroscopic examination has been performed on L. L., who is now 18. The gastroscopic findings were those of a severe atrophic gastritis, which is often observed in patients with pernicious anemia.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1947 to July 1948

JOSEPH B KIRSNER, M D

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CHICAGO

(Concluded from Page 354)

TABLE OF CONTENTS

12 Parasitic and Diarrheal Diseases	Proctosigmoidoscopy
Diagnostic Measures	Volvulus
Food Poisoning	Diverticulosis and Diverticulitis
Epidemic Gastroenteritis	Megacolon
Gastroenteritis in Children	Microcolon
Salmonella Infections	Functional Disorders
Bacillary Dysentery	Ulcerative Colitis
Miscellaneous Observations on	Tuberculosis
Dysentery	Endometriosis
Polioomyelitis Virus	Radiation Injury
Effect of Streptomycin	Perforation
Gastrointestinal Parasites	Sulfonamide and Antibiotic Drugs
Amebiasis	Miscellaneous Conditions
Schistosomiasis	Polyps and Other Tumors
13 Appendix	Carcinoma
Roentgenologic Examination	Colostomy
Appendicitis	15 Anus and Rectum
Intussusception	Congenital Anomalies
Mucocoele	Pruritus Ani
Diverticula	Fissures and Fistulas
Tumors	Hemorrhoids
14 Colon	Rectal Prolapse
Physiologic Studies	War Wounds
Anatomic Studies	Anorectal Surgery
Gas	Miscellaneous Conditions
Laxative	Extrinsic Lesions
Output of Fat and Nitrogen	Tumors
Roentgenologic Examination	

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, The School of Medicine

16 Miscellaneous Gastrointestinal Subjects	Abdominal Pain
Olfactory Acuity and Appetite	Abdominal Epilepsy
Anorexia Nervosa	War Wounds and Abdominal Surgery
Total Intravenous Alimentation	Hernia
Foods and Dyspepsia	Pilonidal Cysts
Psychosomatic Factors in Gastrointestinal Disease	Conditions Involving the Peritoneum
Diagnosis of Gastrointestinal Disease	Conditions Involving the Mesentery
Incidence of Gastrointestinal Disease	Endometriosis
Anemia in Gastrointestinal Disease	Carcinomatous Metastases
Congenital Anomalies	Adhesions
Conditions of the Mouth	Acute Porphyria

PARASITIC AND DIARRHEAL DISEASES

Diagnostic Measures—The laboratory aspects of diagnosis are discussed by several authors.⁷³⁰ Harrison and Banvard⁷³¹ determined fecal antibody titers in a variety of enteric infections. Positive cultures were obtained from 47 per cent of patients studied and, curiously, fecal agglutinins for the organisms studied were found in 96.7 per cent of cases. In chronic ulcerative colitis, relatively high titer fecal agglutinations for at least one species of *Shigella* were present during episodes of exacerbation.

Felsen⁷³² describes a tube for the aspiration of material from rectal mucosal cysts without the aid of a sigmoidoscope. Changes in media are suggested.⁷³³ A simple technic for the culture of enteric pathogens from clotted blood is described, obviating the need for serum, from the patient, which may contain antibodies against an organism.⁷³⁴ Rectal swabs are suggested for the isolation of typhoid bacilli.⁷³⁵ An ingenious

730 Lamb, W. L. The Investigation of Chronic Diarrhea in Adults, *Edinburgh M. J.* **55** 203, 1948. D'Antoni, J. S. Chronic Diarrheas, *Am. J. Surg.* **75**:332, 1948. Cantor, A. J. Bacteriology of Diarrhoeal Diseases, *Am. J. Digest Dis.* **15** 60, 1948. Diagnostic Techniques in Diarrhoea, *ibid.* **15** 88, 1948. Treatment of Diarrhoea, *ibid.* **15** 120, 1948. Felsenfeld, O., and Young, V. M. Comments on Laboratory Diagnosis of Enteric Infections, *ibid.* **14** 392, 1947.

731 Harrison, P. E., and Banvard, J. Coproantibody Excretion During Enteric Infections, *Science* **106** 188, 1947.

732 Felsen, J. New Rectal Culture Tube, *Science* **106** 275, 1947.

733 Taft, E. B., and Daly, A. K. Modified Eosin-Methylene Blue Agar as a Selective Medium for the Primary Isolation of Pathogenic Intestinal Bacteria, *Am. J. Clin. Path.* **17** 561, 1947. Bohls, S. W. Laboratory Aids in the Diagnosis of Infectious Diarrhea in Children, *Texas State J. Med.* **43** 575, 1948.

734 Rappaport, F. Simplified Technic for Culture from Blood of Enteric Groups of Bacteria, *Am. J. Clin. Path.* **17** 904, 1947.

735 Stock, A. H., Warner, F. B., Catto, A. F., and Ashute, A. Rectal Swab Method for Isolating *Eberthella Typhosa*, *Am. J. Clin. Path.* **17** 759, 1947.

method for obtaining suspensions of flagellar antigens and for phase suppression in a single incubation is presented.⁷³⁶

Food Poisoning—In cream filling, one strain of *Staphylococcus aureus* apparently survived for thirty minutes at 55 C and was destroyed in less than three minutes of heating at 85 C.⁷³⁷

An epidemic of food poisoning, due to *staphylococcus enterotoxin* elaborated in a chicken salad, affected 43 men of a 790 man detachment⁷³⁸, another epidemic involving 171 persons was traced to contaminated trifle.⁷³⁹

An outbreak of acute gastroenteritis of unknown etiology occurred in the population of a graduate school.⁷⁴⁰ Werch⁷⁴¹ properly emphasizes the importance of identifying the causative agent whenever possible.

Buchbinder, Osler and Steffen⁷⁴² implicate enterococci as the possible causative organism in four outbreaks of a relatively mild type of food poisoning. Symptoms were produced in 6, or possibly 7, of 26 human volunteers who ate foods in which strains of *Streptococcus faecalis* had grown for five hours.⁷⁴³ Attempts to produce similar symptoms with twenty hour cultures were unsuccessful.

Epidemic Gastroenteritis.—Epidemic gastroenteritis was transmitted to human volunteers by the oral administration of fecal filtrates.⁷⁴⁴ The clinical features of the disease are reviewed by Jaffe.⁷⁴⁵

Gastroenteritis in Children—Two epidemics of diarrhea in infants, occurring at a hospital in Portland, Ore., are analyzed by Lagozzino.⁷⁴⁶ An etiologic bacterial agent was not discovered, the possibility of a

736 Kuhn, L. R. Rapid Method for Producing Suspensions of Flagellar Antigens, and Inducing Phase Suppression, *Am J Clin Path* **17** 569, 1947

737 Hussemann, D. L., and Tanner, F. W. Relation of Certain Cooking Procedures to *Staphylococcus* Food Poisoning, *Am J Pub Health* **37**:1407, 1947

738 Reich, N. E. Epidemiology of a Food Poisoning Epidemic (*Staphylococcus Enterotoxin*), *Am J Digest Dis* **14** 238, 1947

739 Ritchie, J. M., Murray, D. L., and Holgate, M. An Outbreak of *Staphylococcal* Food-Poisoning, *Lancet* **2** 256, 1947

740 Pond, M. A., and Hathaway, J. S. An Epidemic of Mild Gastroenteritis of Unknown Etiology, Presumably Spread by Contaminated Eating Utensils, *Am J Pub Health* **37** 1402, 1947

741 Werch, S. C. The Treatment of Bacterial Food Poisoning, *Bull U S Army M Dept* **8** 199, 1948

742 Buchbinder, L., Osler, A. G., and Steffen, G. I. The Isolation of Enterococci from Foods Implicated in Several Outbreaks of Food Poisoning, *Pub Health Rep* **63** 109, 1948

743 Osler, A. G., Buchbinder, L., and Steffen, G. I. Experimental Enterococcal Food Poisoning in Man, *Proc Soc Exper Biol & Med* **67** 456, 1948

744 Gordon, I., Ingraham, H. S., and Korn, R. F. Transmissions of Epidemic Gastroenteritis to Human Volunteers by Oral Administration of Fecal Filtrates, *J Exper Med* **86** 409, 1947

745 Jaffe, N. B. Epidemic Gastroenteritis, *Am J Digest Dis* **15** 131, 1948

746 Lagozzino, D. A. Epidemic Infantile Diarrhea, *Northwest Med* **47** 40 1948

virus infection was under investigation at the time of writing. There was a lack of response to chemotherapy and to administration of antibiotic drugs. Strict control measures and vigorous parenteral therapy were essential for recovery. Autopsies revealed no characteristic findings, the gastrointestinal tracts were devoid of ulcerative or inflammatory lesions.

Giedt⁷⁴⁷ states the belief that the etiologic agent is likely to be introduced into nurseries under the present methods of caring for infants en masse, and that such infections may be controlled by strict isolation. A specific virus etiology for five epidemics is considered to have been established, but there is need for a practical method of demonstrating the viral cause of an epidemic⁷⁴⁸. In a large percentage of outbreaks, trained investigators have found evidence of gross breaks in nursery technique. Many epidemics have been traced to a variety of pathogenic organisms that could only have reached the infants by the fecal-oral route, some were associated with infections of the upper respiratory tract⁷⁴⁹. A serologically homologous strain of *Escherichia coli* was isolated in 90 per cent of 159 cases of diarrhea in infants, however, the etiologic significance of this organism was not established conclusively⁷⁵⁰. An outbreak is described by Cooke and Marmion⁷⁵¹.

An epidemic in 24 newborn children, with 9 deaths, was traced to milk contaminated with *Pseudomonas aeruginosa*⁷⁵². The presence of this organism in the blood is reported⁷⁵³. The susceptibility of very young children is stressed by Schaffer and Oppenheimer⁷⁵⁴. The death rate in edematous infants was 31.4 per cent, as compared with 17.7 per cent in the nonedematous⁷⁵⁵.

747 Giedt, W. R. Public Health Aspects of Diarrhea of the Newborn, *Northwest Med* **47** 35, 1948.

748 Clifford, S. H. Diarrhea of the Newborn, *New England J Med* **237** 969, 1947.

749 Hinden, E. Etiological Aspects of Gastro-Enteritis, *Arch Dis Childhood* **23** 27, 1948.

750 Giles, C., and Sangster, G. Outbreak of Infantile Gastro-Enteritis in Aberdeen. Association of Special Type of Bact. Coli with Infection, *J Hyg* **46** 1, 1948.

751 Cooke, G. T., and Marmion, B. P. Gastroenteritis of Unknown Etiology, *Brit M J* **2** 447, 1947.

752 Hunter, C. A., and Ensign, P. R. An Epidemic of Diarrhea in a New-Born Nursery Caused by *Pseudomonas Aeruginosa*, *Am J Pub Health* **37** 1166, 1947.

753 Kerby, G. P. *Pseudomonas Aeruginosa* Bacteremia. Summary of Literature, with Report of Case, *Am J Dis Child* **74** 610 (Nov) 1947.

754 Schaffer, A. J., and Oppenheimer, E. H. *Pseudomonas (Pyocyaneus)* Infection of the Gastrointestinal Tract in Infants and Children, *South M J* **41** 460, 1948.

755 Berkeley, J. The Occurrence of Oedema in Infantile Gastroenteritis, *Arch Dis Childhood* **23** 114, 1948.

In Cuba, infections with *Salmonella* and *Shigella dysenteriae* reach epidemic proportions regularly during the summer months⁷⁵⁶ Culture of the feces is essential to accurate diagnosis Sulfadiazine is usually the drug of choice Other antibiotic drugs are indicated when organisms susceptible to other agents have been identified Feldman and Anderson⁷⁵⁷ state that until the etiology is discovered, treatment consists chiefly in the restoration and maintenance of fluid and electrolyte balance, sulfonamide drugs, penicillin and gamma globulin have not yielded striking results Leisti⁷⁵⁸ concludes that streptomycin is advantageous Continuous drip feeding through a nasal catheter is advocated by Berkeley⁷⁵⁹

Salmonella Infections—A brief method is recommended for the identification of *Shigellae* and other *Salmonellae*⁷⁶⁰ Serologic reactions are reviewed by Crosnier and Bernier⁷⁶¹ Young and Felsenfeld⁷⁶² discuss the Vi antigen in the immunology of typhoid fever

Experiments with the feeding of *Salmonella typhimurium* to guinea pigs, rats and mice indicated the relative insignificance of the antigenic component in the localization in Peyer's patches⁷⁶³

All of approximately one hundred and fifty known species of *Salmonella* are pathogenic for man or animals⁷⁶⁴ Clinical manifestations in man include typhoid-like fever, septicemia, acute or chronic enteritis, and localized inflammation, chiefly involving the gallbladder, urogenital organs and bones Some strains tend to produce one clinical picture more often than another The general mortality is approximately 6 per cent

Chesley and Woolsey⁷⁶⁵ report the sporadic occurrence of salmonella infections in Chicago throughout the year, with greater frequency in

756 Hurtado, F, and Aball, A J Acute Diarrhea in Infancy and Childhood, South M J 40 577, 1947

757 Feldman, F, and Anderson, J T Epidemic Diarrhea of the Newborn, Arch Pediat 64 341, 1947

758 Leisti, P Treatment of Infantile Diarrhea by Streptomycin, Ann med int Fenniae 36:575, 1947

759 Berkeley, J Intra-Gastric Drip Feeding in the Treatment of Infantile Gastro-Enteritis, Glasgow M J 28 224, 1947

760 Felsenfeld, O, and Young, V M A Short Procedure for the Isolation and Preliminary Identification of *Shigellae* and *Salmonellae* from Stools, J Trop Med 50 131, 1947

761 Crosnier and Bernier Le séro-diagnostic qualitatif des salmonelloses, France med 8:3, 1947

762 Young, V M, and Felsenfeld, O The Importance of the Vi Antigen, Am J Digest Dis 14 349, 1947

763 Angrist, A, and Mollov, M Morphologic Studies of the Intestine in *Salmonella* Infection in Guinea Pigs and Mice, Am J M Sc 215 149, 1948

764 Felsenfeld, O *Salmonella* Infections in Man, editorial, Am J Clin Path 18 513, 1948

765 Chesley, F F, and Woolsey, C I *Salmonella* Infections at the Cook County Hospital, Chicago, Illinois, Gastroenterology 9:177, 1947

the summer and autumn months, such infection was diagnosed in 154 cases during the period from 1936 to 1945, the mortality was 65 per cent. The majority of deaths occurred in infants, the principal causes being appendicitis, peritonitis or bronchopneumonia. Smith⁷⁶⁶ emphasizes the diagnostic value of the proctosigmoidoscopic examination. Sulfadiazine was found to be moderately effective in treatment.

Three related outbreaks of infection with *S. typhimurium* are reported⁷⁶⁷. The oral administration of streptomycin is considered of value in altering the bacterial flora and preventing extension of the infection. Thirty-three cases of sporadic salmonellosis, with ten different types of *Salmonella*, are evaluated⁷⁶⁸. Invasion of the blood stream was detected in 6 cases, reaction to the Widal test was positive in 7 of 16. The clinical symptoms were diarrhea in 27 cases, fever, 1 case, septicemia and osteomyelitis, 1 case, septicemia and meningitis, 1 case, and bacteremia complicating other diseases, 2 cases, the patient in 1 case was a carrier. Among 219 cases of *Salmonella* infection in Panama during the years 1942 to 1946, thirty different types of organisms were identified, *S. typhimurium*, *Salmonella newport* and *Salmonella montevideo* were the most common⁷⁶⁹. The clinical and pathologic features in 14 cases of *Salmonella blegdam* infection in natives of New Guinea are described⁷⁷⁰. Severe acute hemolytic anemia was a feature in several instances. Two new *Salmonella* types, *Salmonella hidalgo* and *Salmonella mission*, are described by Watt and others⁷⁷¹ and *Salmonella chittagong*, by Taylor and his co-workers⁷⁷². Another new type of *Salmonella*, *Salmonella fayed*, was isolated in a fatal case of bacterial endocarditis⁷⁷³. An epidemic in Helsingfors was caused by *Salmonella enteritidis danysz*, transmitted by milk⁷⁷⁴.

766 Smith, L. A. *Salmonellosis: Experiences in Military and Civilian Practice*, Gastroenterology **9** 551, 1947.

767 Abramson, H. *Infection with Salmonella Typhimurium in the Newborn*, Am J Digest Dis **74** 576, 1947.

768 Neter, E. *Microbiological Aspects of Salmonellosis in Children*, New York State J Med **48** 412, 1948.

769 Henderson, L. L. *Salmonella Infections in Panama*, Am J Trop Med **27** 643, 1947.

770 Jones, H. I., and Fenner, F. *Infection with Salmonella Blegdam Amongst Natives of New Guinea*, M J Australia **2** 356, 1947.

771 Watt, J., DeCapito, T. M., Edwards, P. R., and Moran, A. B. *Two New Salmonella Types: Salmonella Hidalgo and Salmonella Mission*, Pub Health Rep **63** 223, 1948.

772 Taylor, J., Hayes, W., Freeman, J., and Anderson, E. S. *New Salmonella Type: Salmonella Chittagong*, J Path & Bact **60** 35, 1948.

773 Anderson, E. S., Anderson, H. J., and Taylor, J. *A New Salmonella Which Caused Fatal Endocarditis in Man*, J Path & Bact **59** 533, 1947.

774 Kokko, U. P. *Gastroenteritis Epidemic Due to Salmonella Enteritidis Var Danysz (Ratin)*, Nord med **36** 2325, 1947.

In an outbreak due to *S. montevideo*, 19 patients (6 per cent) showed evidence of bronchopulmonary involvement⁷⁷⁵ Four had acute bronchitis One patient, whose case was described in detail, had definite bronchopneumonia, with sputum containing the *Salmonella* organism The other 14 patients had interstitial pneumonia

Henderson⁷⁷⁶ describes meningitis due to *Salmonella* in 3 infants, 1 of whom recovered A review of the literature indicates that the disease is favorably influenced by systematic treatment with sulfonamide drugs, sulfadiazine probably being the drug of choice Penicillin is ineffective Anchersen⁷⁷⁷ describes the occurrence of osteomyelitis of the spine, psoas abscess and lumbar abscess in a man eighteen years after his having enteric fever, during which *Salmonella paratyphi B* was cultured from the feces After thirteen additional years, the same organism was cultured in pus from the abscess In an outbreak among troops in New Guinea, focal suppuration eventually developed in all of 6 patients with late manifestations⁷⁷⁸ Silverman and Leslie⁷⁷⁹ encountered 16 cases of chronic dysentery due to *Salmonella*, clinically indistinguishable from that due to *Shigella dysenteriae* A terminal *Salmonella* infection occurred in a woman of 69 with presenile sclerosis (Alzheimer's disease)⁷⁸⁰

Bacillary Dysentery—Tal and Olitzki⁷⁸¹ studied the toxic and antigenic properties of fractions prepared from the complete antigen of *Sh. dysenteriae*

Cooper and Keller⁷⁸² present data regarding two methods for testing the passive protective power for mice of serums from subjects

775 Ingegno, A P , D'Albora, J B , Edson, J N , and Gianquinto, P J Pneumonia Associated with Acute Salmonellosis, *Arch Int Med* **81**:476 (April) 1948

776 Henderson, L L *Salmonella Meningitis Report of Three Cases and Review of One Hundred and Forty-Four Cases from Literature*, *Am J Dis Child* **75** 341 (March) 1948

777 Anchersen, P A Case of Spondylitis Caused by *Salmonella Paratyphi B*, *Nord med* **36** 2019, 1947

778 Baker, M P , and Bragdon, J H Septicemia Due to *Salmonella Enteritidis*, *New England J Med* **237** 175, 1947

779 Silverman, D N , and Leshe, A *Salmonella—a Cause of Chronic Bacterial Dysentery*, *Gastroenterology* **9** 562, 1947

780 Himmelboch, E , Latham, O , and McDonald, G C Alzheimer's Disease Complicated by a Terminal *Salmonella* Infection, *M J Australia* **34** 701, 1947

781 Tal, C , and Olitzki, L The Toxic and Antigenic Properties of Fractions Prepared from the Complete Antigen of *Shigella Dysenteriae*, *J Immunol* **58** 337, 1948

782 Cooper, M L , and Keller, H M Studies in Dysentery Vaccination I The Passive Mouse Protection Test, II Humoral Antibody Content of Sera, III Immunity in Mice Injected with Vaccines of *Shigella* from Children Convalescent from Dysentery, *J Immunol* **58** 349, 1948

receiving *Shigella* vaccines Active immunized mice consistently demonstrated a higher degree of homologous immunity than of heterologous immunity

Eleven strains of *Escherichia coli*, antagonistic in the living state to *Shigella paradysenteriae*, Flexner type III, produced antibiotic substances when grown on the surface of agar media, whereas four strains, nonantagonistic in the living state, did not do so⁷⁸³ The properties of the antibiotic substance of one strain, *Esch coli* 534, were similar to those of the substance which was described by Heatley and Florey (*Brit J Exper Path* 27: 378, 1946)

Shigella sonnei, given by gavage to white mice, were found within five to thirty minutes in cultures of the spleen, liver, kidneys, central mesenteric glands, lungs and heart of the majority of mice, but were seldom cultured from these tissues after two hours⁷⁸⁴ Experimental infection of mice with *Sh dysenteriae*, in the presence of mucin, may be modified by the administration of either an antitoxic or an antibactericidal serum⁷⁸⁵ Antibactericidal serum acts directly by lysis of the bacteria but does not prevent intoxication due to the liberated toxin

In 1,826 positive cultures obtained from approximately 21,000 specimens of stools, fifteen serologic types of bacilli causing dysentery were identified⁷⁸⁶ An outbreak of dysentery was attributed to a new type of organism, given the imposing designation of Type T-2nd Medical Lab or Lovington I or Etousa⁷⁸⁷ Person to person contact is believed to have been the most important factor in the transmission of an epidemic in French Morocco during 1943, food handlers were likely vectors⁷⁸⁸ The distribution of positive cultures obtained in an

783 Halbert, S P, and Magnuson, H J Studies with Antibiotic-Producing Strains of *Escherichia Coli*, *J Immunol* 58 397, 1948

784 Cooper, M L, and Keller, H M Invasion by *Shigella Sonnei* of Tissues of Mice Following Gavage with Viable *Shigella*, *Proc Soc Exper Biol & Med* 68 87, 1948

785 Oltzki, L, Koch, P K, and Shelubsky, M Experimental Infection of Mice with *Shigella Dysenteriae* and Modification of the Infection by Means of Antitoxic and Antibacterial Sera, *Exper Med & Surg* 5 206, 1947

786 Stock, A H, Eisenstadt, I, Triplett, G W Jr, and Catto, A Field Studies in Bacillary Dysentery in U S Military Personnel and Civilians in North Africa and Italy I Types of Dysentery Bacilli Isolated from U S Army Personnel and Natives in French Morocco and Italy, *J Infect Dis* 81 59, 1947

787 Stock, A H, Tribby, W W, and Ashute, A Field Studies in Bacillary Dysentery in U S Military Personnel and Civilians in North Africa and Italy II Pathogenicity of a New Serologic Type of Dysentery Bacillus (T-2nd Med Lab or Lovington I or Etousa), *J Infect Dis* 81 65, 1947

788 Stock, A H, Karlson, A G, Tribby, W W, and Hill, J H Field Studies in Bacillary Dysentery in U S Military Personnel and Civilians in North Africa and Italy III The Epidemic of Bacillary Dysentery in the Atlantic Base Section, French Morocco, 1943, *J Infect Dis* 81 68, 1947

outbreak of dysentery among United States troops engaged in the assault on the Gothic line indicated that the outbreaks were at least partly bacterial in origin⁷⁸⁹ Division food handlers were often found to be infected Six per cent of Italian civilians examined during the fall of 1941 were found to be carriers

Dysentery affecting 326 persons aboard a cruiser in Apra harbor, Guam, was related to *Sh. flexneri* III⁷⁹⁰ The source is considered to have been a backflow of sea water in the dishwashing machine A wide variety of *Shigella* organisms were identified in Japan during the summer of 1947⁷⁹¹ Observations on dysentery in Japanese civilian prison camps in the Philippines are made by Haughwout⁷⁹²

Young and McEwen⁷⁹³ studied 14 cases of postdysenteric arthritis in 1943 in Algeria The condition of 7 of the patients in these cases fulfilled the clinical criteria for the "uretero-conjunctivo-synovial syndrome" of Fiessinger and Heray, the syndrome is the same as that in Reiter's disease, namely, the combined occurrence of three recognized complications of bacillary dysentery arthritis, urethritis and conjunctivitis Perforation of the colon occurred in cases of bacillary and amebic dysentery⁷⁹⁴ *Sh. paradysenteriae* was isolated from the gallbladder at autopsy in 3 fatal cases⁷⁹⁵ Herrlick⁷⁹⁶ reports the development of polyneuritis Present *Shigella* vaccines given parenterally are ineffective in the prevention of naturally occurring infections⁷⁹⁷ VanGelder,

789 Stock, A H, Warner, F B, and Levinson, H S Field Studies in Bacillary Dysentery in U S Military Personnel and Civilians in North Africa and Italy IV Distribution of Dysentery Bacilli Types in U S Troops Before, During and After the Assault on the Gothic Line, *J Infect Dis* **81** 72, 1947

790 Mount, R A, and Floyd, T M A Dysentery Outbreak Aboard a Cruiser in Apra Harbor, Guam, *U S Nav M Bull* **48**:240, 1948

791 Barksdale, W L *Shigellae* Occurring in Japan, *Am J Trop Med* **28**:359, 1948

792 Haughwout, F G Dysentery, Colitis, and Diarrhea in Japanese Civilian Prison Camps in the Philippines During World War II I Primary, Concurrent, and Recurrent Dysentery, *Am J Digest Dis* **15** 142, 1948, II Post-Dysenteric and Non-Dysenteric Animal Parasites, *ibid* **15** 176, 1948

793 Young, R H, and McEwen, E G Bacillary Dysentery as the Cause of Reiter's Syndrome (Arthritis with Nonspecific Urethritis and Conjunctivitis), *J A M A* **134** 1456 (Aug 23) 1947

794 Bingham, J A W Perforation of the Colon in Dysentery, *Lancet* **1** 139, 1948

795 Van der Sar, A, Pot, A W, and Hartz, P H Isolation of *Shigella* from the Gallbladder in Bacillary Dysentery, *Am J Clin. Path* **18** 509, 1948

796 Herrlick, A Polyneuritis After Bacillary Dysentery, *Nervenarzt* **19** 167, 1948

797 Hardy, A V, DeCapito, T, and Halbert, S P Studies of the Acute Diarrheal Diseases Immunization in Shigellosis, *Pub Health Rep* **63** 685, 1948

Daines and Fischer⁷⁹⁸ point out that persistent *Shigella* carriers can become important epidemiologically. The strain of *Sh. flexneri* III (VIII) isolated from these carriers proved to be highly resistant to the bacteriostatic action of sulfadiazine but was very sensitive to the action of streptomycin in vitro. The intermittency of obtaining positive cultures from carriers makes it difficult to establish a bacteriologic cure. Twelve consecutive negative cultures are probably a fairly adequate criterion. Cultures from rectal swabs in clinical cases and from asymptomatic carriers demonstrated an alternation of positive and negative cultural phases over periods ranging up to two hundred and two days.⁷⁹⁹ A total dose of 1.5 Gm. of streptomycin had no appreciable effect, but 30 Gm. of the drug, given over a ten day period, resulted in an apparent cure, the organisms were resistant to sulfonamide drugs. However, they may be of value in some cases.⁸⁰⁰

Miscellaneous Observations on Dysentery—In 123 unselected cases of chronic enteric disease caused by *Endamoeba histolytica*, *Sh. dysenteriae* and *Salmonella paratyphi*, diarrhea constituted the chief complaint in only 13, there apparently was no history of diarrhea in 44.⁸⁰¹ Meyers and Payne,⁸⁰² in 280 cases of diarrhea noted amebiasis, bacillary dysentery, *Salmonella* infections, giardiasis and helminthic infection, so-called psychosomatic diarrhea was the most frequent cause, occurring in 20.5 per cent, a considerable number of infections with diarrhea, but without demonstrable etiology, were considered as possible residual infections following bacillary dysentery, amebiasis or *Salmonella* infection, or of virus origin. Rappaport⁸⁰³ incriminates milk as the allergic cause of persistent diarrhea in 40 of 67 cases.

Shigella alcalescens was cultured from the blood and urine of a young woman with symptoms of pyelocystitis, diarrhea, and chills and fever.⁸⁰⁴ The organism was sensitive to sulfadiazine and the infection

798 VanGelder, D. W., Daines, W. P., and Fischer, G. L. *Shigella Carriers with Special Reference to Their Therapy, Including the Use of Streptomycin*, *Am J Trop Med* **27**: 225, 1947.

799 Philbrook, F. R., Barnes, L. A., McCann, W. J., and Harrison, R. R. *Prolonged Laboratory Observations on Clinical Cases and Carriers of "Shigella Flexneri III" Following an Epidemic*, *U S Nav M Bull* **48**: 405, 1948.

800 Bassler, A., and Peters, A. G. *Sulfonamide Therapy of Infections of the Gastrointestinal Tract*, *Rev Gastroenterol* **15**: 151, 1948.

801 Silverman, D. N., and Leslie, A. *Enteric Infection of Infestation Sine Dysentery*, *New Orleans M & S J* **100**: 101, 1947.

802 Meyers, S. G., and Payne, C. A. *Diarrhea in U S Army Personnel in Italy*, *Gastroenterology* **9**: 186, 1947.

803 Rappaport, E. A. *Post-Dysenteric Diarrhea Due to Milk Allergy*, *Rev Gastroenterol* **15**: 466, 1948.

804 Cardon, L., and Felsenfeld, O. *A Case of Shigella Alcalescens Cystopyelitis and Bacteremia*, *Am J Clin Path* **18**: 55, 1948.

was cured with it. Agglutinins to the organism developed several weeks later.

Darnall⁸⁰⁵ reports 4 cases in which the syndromes of chronic dysentery were closely associated with the findings of paracolon bacilli in the feces. Streptomycin therapy eliminated the suspected bacilli and resulted in clinical cure or improvement. Eleven additional patients, with somewhat similar symptoms, were also found to be harboring paracolon bacilli. Antigenic analysis of the sixteen different paracolon organisms isolated in this series revealed the presence of *Salmonella* or *Shigella* antigens in nearly 70 per cent of cases. A possible relation between paracolon infections and obscure chronic diseases is mentioned.

An outbreak of acute enteric disease, occurring in 80 of 250 diners served fricasseed chicken in an Army officers' mess, was attributed to a paracolon organism resembling the one designated by Stuart as "29911"⁸⁰⁶

Poliomyelitis Virus—According to Faber and others,⁸⁰⁷ the gastrointestinal tract appears to be relatively impermeable to the virus and may be regarded as an exceptional portal of infection.

Effect of Streptomycin—Streptomycin, given in doses of 1 or 2 Gm daily by mouth to 5 patients, and as a lavage of the distal loop of bowel through a colostomy to another, eliminated *Esch coli* within two days, there was no effect on the streptococci or anaerobic flora of the feces⁸⁰⁸. In vivo levels did not inhibit four strains of *Bacillus funduliformis* and eight of *Bacillus fragilis* in vitro⁸⁰⁹. *Ps aeruginosa* and *Bacillus subtilis* were stimulated by artificial media containing streptomycin⁸¹⁰. Laboratory and clinical studies indicate that the drug is of little value in the treatment of peritonitis⁸¹¹. Certain

805 Darnall, C L. Paracolon Bacilli as Related to Chronic Dysentery Syndromes, *Gastroenterology* **10** 366, 1948.

806 Plass, H F R. Outbreak of Diarrheal Disease Associated with Paracolon, *J Lab & Clin Med* **32** 886, 1947.

807 Faber, H K, Silverberg, R J, and Dong, L. Poliomyelitis in the Cynomolgus Monkey. IV. Further Observations on Exposures Confined to the Stomach and Intestines with Notes on Fecal Excretion of Virus, *J Exper Med* **88** 65, 1948.

808 Kane, L W, and Foley, G E. Effect of Oral Streptomycin on the Intestinal Flora, *Proc Soc Exper Biol & Med* **66** 201, 1947.

809 Foley, G E. In Vitro Resistance of the Genus *Bacteroides* to Streptomycin, *Science* **106** 423, 1947.

810 Kushnick, T, Randles, C I, Gray, C T, and Birkeland, J M. Variants of *Escherichia Coli*, *Pseudomonas Aeruginosa*, and *Bacillus Subtilis* Requiring Streptomycin, *Science* **106** 587, 1947.

811 Silvan, H L, Rothenberg, S, Warmer, H, Amluxen, J, and McCorkle, H J. Laboratory and Clinical Experiences with Streptomycin Therapy in the Management of Infections of Intestinal Origin, *Surg, Gynec & Obst* **85** 721, 1947.

enteritides due to *Salmonella* and *Shigella* organisms responded favorably to streptomycin, but the results were equivocal in nonspecific ulcerative colitis, the drug was ineffective in typhoid⁸¹² Infantile diarrhea, in general, seemed to respond well, in some cases dramatically

Gastrointestinal Parasites—Tompkins and Miller⁸¹³ present a rapid method for staining intestinal protozoa, utilizing iron hematoxylin-phosphotungstic acid stain The value of the zinc sulfate flotation technic for the isolation of protozoa from feces is emphasized⁸¹⁴

The mucosal pattern of parasitic infections of the colon was studied roentgenologically, widening and derangement of folds were present in the cecum, the ascending colon and the sigmoid⁸¹⁵ Warmoes describes the roentgenologic changes occasionally noted in cases of *Ascaris* infection⁸¹⁶

Examination of the feces in approximately 5,500 cases in New York over a period of twenty-eight consecutive months (1944 to 1946) led to the recognition of *E. histolytica* in 254, *Giardia lamblia* in 232, *Balantidium coli* in 5, hookworm in 204, *Trichuris trichiura* in 590, *Ascaris lumbricoides* in 156, *Enterobius vermicularis* in 192, *Strongyloides stercoralis* in 67, *Schistosoma mansoni* in 43, *Taenia saginata* in 21 and *Diphyllobothrium latum* in 3⁸¹⁷

Markel and his associates⁸¹⁸ investigated the incidence of parasites in 1,153 military personnel in the Philippines Of the group, 40.3 per cent were infected with one or more parasites, the most common being *Esch. coli*, *Endolimax nana*, *Endamoeba histolytica* and hookworm Among civilian Navy employees and their families, *T. trichiura* was present in 44.6 per cent, with *E. nana*, *E. histolytica* and *Esch. coli* present in approximately 26 to 36 per cent Civilian personnel employed at Naval air bases in Brazil were found to have a high incidence of intestinal parasites, hookworm, *Ascaris*, *Trichocephalus trichiuris* and *E. histolytica* were present in 71.4, 61.4, 47.4 and 18.8

812 Pulaski, E. J., and Amspacher, W. H. Streptomycin Therapy for Certain Infections of Intestinal Origin, *New England J. Med.* **237** 419, 1947

813 Tompkins, V. N., and Miller, J. K. Staining Intestinal Protozoa with Iron-Hematoxylin-Phosphotungstic Acid, *Am. J. Clin. Path.* **17** 755, 1947

814 Bijlmer, J. On the Recovery of Protozoa and Eggs of Some Species of Helminths in Human Feces, *J. Parasitol.* **34** 101, 1948

815 Arendt, J., and Coheen, J. Mucosal Studies in Colitis Due to Parasites, *Am. J. Roentgenol.* **59** 865, 1948

816 Warmoes, F. Intérêt de l'examen Radiologique dans certains cas d'ascaridiose, *Acta gastroent. belg.* **11** 148, 1948

817 Shookhoff, H. B. Intestinal Parasitosis in the Civilian Population, *Rev. Gastroenterol.* **14** 547, 1947

818 Markel, E. K., Mullinger, P. E., and Schneider, D. J. Intestinal Parasitic Infections in Naval Personnel, *Am. J. Trop. Med.* **27** 63, 1947

per cent, respectively⁸¹⁹ Eighty-six per cent of 400 soldiers who had been prisoners of the Japanese were found to be harboring intestinal parasites, 76 per cent harbored parasites generally considered to be pathogenic⁸²⁰ *T trichiura* was found in 40 per cent, *A lumbricoides* and hookworm, in 35 per cent each, *Esch coli*, in 32 per cent, *E nana*, in 15 per cent, and *E histolytica*, in 110 per cent As might have been expected, a higher percentage of pathogenic parasites was found in Canadian prisoners of war repatriated from Hong Kong than among Canadian civilians⁸²¹

Examination of a single specimen of feces from each of 600 adult inhabitants of San Juan, Puerto Rico, demonstrated *E histolytica* in 17.3 per cent⁸²²

The incidence of *G lamblia* infection in children from 1 to 3 (on admission to a nursery) was 26.6 per cent⁸²³ The great majority of "long stay" children in this nursery were similarly infested There appeared to be no definite relation between the occurrence of *Giardia* infection and the onset of loose stools Dietetic upsets, infections, especially of the upper respiratory tract, and psychologic disturbances probably were the important factors predisposing to the onset of diarrhea

In a study of 8,017 white school children in Florida, Hood⁸²⁴ noted hookworm infection in 40 per cent, the incidence was very low in a group of 1,264 Negro children Among servicemen returning from the Pacific, 1 in 15 has been reported infected with *Ancylostoma duodenale*⁸²⁵ Advanced changes in the small bowel were demonstrated in the case of a patient with hookworm infection, minimal alterations were noted in a second case⁸²⁶ Of 46 patients with hookworm disease, admitted to a hospital because of symptoms, 23 complained of abdominal

819 MacCreary, D, and Bricker, A G The Incidence of Intestinal Parasites Among Civilians Employed at Certain Naval Air Bases, U S Nav M Bull **47** 926, 1947

820 May, E L Parasitologic Study of Four Hundred Soldiers Interned by the Japanese, Am J Trop Med **27**:129, 1947

821 Starlsey, H, and Poole, J Survey of Intestinal Parasites in Repatriated Prisoners of War from Hong Kong, Canad M A J **57** 377, 1947

822 Young, V M, and Felsenfeld, O The Occurrence of Intestinal Protozoa in Adults in San Juan, Puerto Rico, J Parasitol **34** 229, 1948

823 Brown, E H *Giardia Lamblia* The Incidence and Results of Infestation of Children in Residential Nurseries, Arch Dis Childhood **23** 119, 1948

824 Hood, M The Present Status of Hookworm Infection in Florida, Am J Trop Med **27** 505, 1947

825 Loughlin, E H, and Stoll, N R Hookworm Infections in American Servicemen with Reference to Establishment of *Ancylostoma Duodenale* in Southern United States, J A M A **136** 157 (Jan 17) 1948

826 Khoo, F Y, and Chiang, H S Hookworm Disease Showing Abnormal Roentgenologic Small Intestine Changes, Chinese M J **65** 349, 1947

pain⁸²⁷ Four of these were operated on, with a diagnosis of appendicitis One patient had a perforated appendix, with peritonitis, the hookworm infestation being incidental Cruz and Pimenta de Mello⁸²⁸ state that it is possible to maintain normal blood values in patients severely infected with *Ancylostoma* or *Necator* by the administration of a sufficient quantity of iron The minimum dose necessary to maintain normality of the blood in a person weighing 45 Kg, with 1,051 helminths, was 0.2 Gm of ferrous sulfate daily

Nine papers in the Scandinavian literature deal with *Bothriocephalus* infection and anemia⁸²⁹ Twenty-four patients were studied at intervals of one to twenty-two years after treatment for *Bothriocephalus* anemia No clear divergence from the normal blood picture was noted Achlorhydria after alcohol and histamine stimulation was noted in 12 cases, in these, only two or three years had elapsed since therapy^{829a} Addition of fresh or dried *D. Bothrium latum* does not nullify the antianemic effect of mixtures of extrinsic and intrinsic factors when given to patients with "cryptogenic" pernicious anemia Administration of dried worm does not hinder the remission after worm cure in pernicious tapeworm anemia^{829b} The presence of free hydrochloric acid in gastric juice differentiates between pernicious tapeworm anemia and "cryptogenic" pernicious anemia in *Diphyllobothrium* carriers^{829c} Complete recovery after worm cure indicates pernicious tapeworm anemia, even when there is no free hydrochloric acid in the gastric juice Liver therapy is sometimes necessary to correct tapeworm anemia, the absence of relapse rules out pernicious anemia Tapeworm carriers with and without pernicious anemia were subjected to intestinal

827 McEwan, D, Economon, J G, and Zellner, R E Mistaken Surgical Diagnoses in Hookworm Disease, *South Surgeon* **13** 760, 1947

828 Cruz, W O, and Pimenta de Mello, R Prophylaxis of Hookworm Anemia-Deficiency Disease, *Blood* **3** 457, 1948

829 (a) Hernberg, C A On the Secretion of Gastric Juice in Recovery After Pernicious *Bothriocephalus* Anemia, *Acta med Scandinav* **129** 12, 1947 (b) von Bonsdorff, B Does Feeding of *Diphyllobothrium Latum* Influence the Interaction Between the Intrinsic and Extrinsic Factors of Castle? *ibid* **129** 59, 1947 (c) Hirvonen, M On the Differential Diagnosis Between Pernicious Tapeworm Anemia and Cryptogenic Pernicious Anemia in Carriers of *Diphyllobothrium Latum*, *Ann med int Fenniae* (supp 2) **35** 1, 1947 (d) von Bonsdorff, B The Site of Infestation with Fish Tapeworm Determined by Means of Intestinal Intubation, *Acta med Scandinav* **129** 213, 1947 (e) von Bonsdorff, B "Castle's Test" in Pernicious Tapeworm Anemia, *ibid*, 1947, supp 196, p 456 (f) Eskola, O On the Amount of Urobilin Excreted in Urine and Feces in Pernicious Tapeworm Anemia and Its Relation to the Reticulocyte Crisis, *Ann med int Fenniae* **37** 1, 1948 (g) Hirvonen, M Observations Throwing Light on the Pathogenesis of Pernicious Tapeworm Anemia, *ibid* **36** 53, 1947 (h) Totterman, G Is the Broad Tapeworm the Causal Agent of Hypochromic Anemia? *ibid* **36** 185, 1947 (i) von Bonsdorff, B In Which Part of the Intestinal Canal Is the Fish Tapeworm Found? *Acta med Scandinav* **129** 142, 1947

intubation^{829d} Patients with manifest pernicious anemia all proved to have worms in the jejunum In cases of nonanemic subjects, patients with anemia of a nonpernicious type and patients with pernicious tapeworm anemia in a state of spontaneous remission, the worm was not found before reaching the ileum The author concludes that when the worm is located high in the intestine it may impair the interaction between extrinsic factor (meat or yeast extract) and intrinsic factor (normal human gastric juice) and thus cause pernicious anemia Administration of mixtures of extrinsic factor and intrinsic factor produces no significant hematologic remission in cases of pernicious tapeworm anemia, whereas liver extract does induce remission It is thought that the presence of the worm in the intestinal canal prevents the interaction between extrinsic and intrinsic factors^{829e} Excretion of urobilin in the feces in pernicious tapeworm anemia was elevated to between 200 and 540 mg and in the urine, to between 2.5 and 10 mg in twenty-four hours After therapy with liver, urobilin excretion rose as high as 1,040 mg in feces and 36 mg in urine, it then fell to normal after ten to nineteen days The findings are interpreted as indicating that hemolysis is a secondary factor in pernicious tapeworm anemia^{829f} Infection with broad tapeworm does not cause hypochromic anemia^{829h}

The findings at operations and at autopsies indicate that *D. latum* is most frequently present in the ileum, rarely in the jejunum and occasionally in the colon The worm can also develop in the gallbladder Emphasis is directed to "tapeworm vomiting" as a characteristic symptom⁸²⁹ⁱ Eleven infections are reported in Jewish women who had tasted *gefulte* fish before cooking⁸³⁰

The growth of *E. nana* was not inhibited by large concentrations of streptomycin in vitro⁸³¹

Living adult trichina worms, including gravid females, were found in the intestine in a fatal case of human trichinosis fifty-four days after ingestion of infected pork The possibility of continued release of larvae over a long period must be taken into account in the management of trichinosis⁸³²

Starkus⁸³³ reports an outbreak of "ulcerative colitis" in the concentration camp at Stutthof In the cases in which results of bacterio-

830 Sandweiss, D. J., and Sugarman, M. H. Fish Tapeworm Infestation Due to Sampling of "Gefulte" Fish or Its Soup Before Adequate Cooking, *J. Michigan M. Soc.* **46** 1156, 1947

831 Pfeiffer, A. V. Effect of Streptomycin on *Endolimax Nana* in Vitro, *J. Parasitol.* **34** 142, 1948

832 Stryker, W. A. The Intestinal Phase of Human Trichinosis, *Am. J. Path.* **23** 819, 1947

833 Starkus, A. Colitis Ulcerosa Fusio-Spirochaetosa, *Gastroenterologia* **72** 35, 1947

logic examination were negative, it was almost invariably possible to demonstrate spirochetes (frequently *Bacillus fusiformis*) Pathologically, the changes resembled those of balantidial colitis or of amebic dysentery Clinically, the disease pursued either a toxic-fulminant or a protracted course In the acute cases, death was due to cardiovascular failure, in the protracted cases, to inanition The death rate was estimated at 95 to 98 per cent, septic complications were found in 7 per cent of the cases in which necropsy was done Administration of neoarsphenamine U S P (neosalvarsan[®]) was very effective, response to the drug was assumed to establish the etiology

Two cases of infection with *Isospora hominis* in soldiers were encountered⁸³⁴ Both patients had mild intermittent diarrhea, malaise, loss of weight and eosinophilia, bismuth salicylate apparently cured 1 and sulfaguanidine, the other The case of another person harboring *I hominis*, but without symptoms,⁸³⁵ is reported

In a case of dysentery due to balantidial colitis, death was attributed to the infection and dehydration⁸³⁶ Sulfathiazole is reported to have rapidly and completely cured 1 infection⁸³⁷

Two cases of ancylostomiasis, with an eosinophil count of approximately 70 per cent, are reported⁸³⁸

Amebiasis—An alcoholic extract cultivation medium tested for three years has been found valuable in cases of infection with *E histolytica*,⁸³⁹ It possesses a good ability to develop positive cultures from small numbers of organisms The addition of streptomycin prolonged the survival of cultures of trophozoites⁸⁴⁰ Agglutination of cysts obtained from culture occurs in dilutions of the blood serum of man and of the horse⁸⁴¹ There appears to be no correlation of this phenomenon with either infection with *E histolytica* or the complement-fixing properties of a serum

834 Kirshbaum, J D Intestinal Coccidiosis, *Am J Clin Path* **18** 58, 1948

835 May, E L *Isospora Hominis* Infection in Man, *Am J Trop Med.* **27** 323, 1947

836 Miller, A A, and Peck, C R Balantidial Dysentery Report of a Fatal Case in Assam, *Brit M J* **1** 448, 1948

837 Hirvonen, M Do Sulphonamides Possibly Have Any Effect on *Balantidium Coli*? *Ann med int Fenniae* **36** 274, 1947

838 Whitehouse, F R Massive Eosinophilia in Uncinariasis Report of Two Cases, *Gastroenterology* **9** 303, 1947

839 Nelson, E C Alcoholic Extract Medium for the Diagnosis and Cultivation of *Endamoeba Histolytica*, *Am J Trop Med* **27** 545, 1947

840 Spingarn, C L, and Edelman, M H The Prolongation of the Viability of Cultures of *E Histolytica* by the Addition of Streptomycin, *J Parasitol* **33** 416, 1948

841 Greif, R L Agglutination of *Endamoeba Histolytica* Cysts, *Am J Trop Med* **27** 131, 1947

Seven of 11 rats from an area of London endemic for amebiasis were found to be infected with organisms morphologically identical with *E. histolytica*. The amebas were restricted to the cecum, but no lesions were present. On injection into the cecum of young rats, the amebas invaded the walls, producing lesions which responded to emetine.⁸⁴²

Dolkart and Hedges,⁸⁴³ in a series of 3,605 cases in the Chicago area, found 0.7 per cent of patients to be infected with *E. histolytica*. In 1,070 cases, with symptoms of the digestive tract, the incidence was 3.5 per cent. Snorff and others⁸⁴⁴ found *E. histolytica* in the feces of 2 per cent of the asymptomatic patients and in 4.31 per cent of those of symptomatic patients. The culture method was found to be superior to that with the direct smear alone. Of the stools examined, 72 per cent were discovered to contain *E. histolytica* in the first examination, 11 per cent, in the second, and 17 per cent, in the third. The incidence of infestation with flagellates or helminths was much lower. The authors state the opinion that returning veterans and prisoners of war have not affected the incidence of infection to date.

Spellberg and Zivin⁸⁴⁵ conclude that there is an increased incidence of active, virulent amebiasis in veterans of World War II. Fifteen hepatic complications were observed in 58 cases. The treatment of choice for hepatitis is administration of emetine, for hepatic abscess, administration of emetine plus aspiration. One unusual case was complicated with a cerebellar abscess. Nicholson and De Dominicis⁸⁴⁶ review 60 cases in New England. Parkinson⁸⁴⁷ states the belief that sulfonamide drugs are helpful in acute amebic dysentery.

Napier⁸⁴⁸ considers the public health aspects of the problem of the cyst passer but offers no solution. The incidence of amebiasis was 20 per cent in American soldiers in the Calcutta area and only 5 per cent in New Delhi, but the incidence of diarrhea did not vary in these groups, suggesting to the authors that infection with paracolon bacilli

842 Neal, R. A. *Entamoeba Histolytica* in Wild Rats Caught in London, *J Hyg* 46:90, 1948.

843 Dolkart, R. E., and Hedges, R. N. The Present Incidence of Intestinal Infestation with *E. Histolytica* and Other Protozoa in the Chicago Area, *Gastroenterology* 9:170, 1947.

844 Snorff, L. D., Foltz, E. E., and Howard, B. A. A Post-War Survey of Amebiasis and Other Intestinal Parasites, *Gastroenterology* 9:539, 1947.

845 Spellberg, M. A., and Zivin, S. Amebiasis in Veterans of World War II with Special Emphasis on Extra-Intestinal Complications, Including a Case of Amebic Cerebellar Abscess, *Gastroenterology* 10:452, 1948.

846 Nicholson, J. H., and De Dominicis, F. A. Amebiasis, *New England J Med* 237:799, 1947.

847 Parkinson, T. Amœbiasis in Ceylon, *Lancet* 2:612, 1947.

848 Napier, L. E. The Cyst Passer, *J Trop Med* 50:169, 1947.

may explain certain nonamebic diarrheas⁸⁴⁹ Sandler⁸⁵⁰ and Groff⁸⁵¹ consider the symptomatology of chronic amebiasis

E. histolytica was found in the feces of 93 children in an orphanage⁸⁵² Relatively little difference was observed in the height, weight, blood counts and clinical findings for the infected group as compared with corresponding values for uninfected children, although a higher percentage of the former complained of fatigue and vague gastrointestinal symptoms Seventy-three children whose stools contained cysts of *E. histolytica* were considered to have alterations in personality, appetite and bowel habits⁸⁵³ The only distinctive physical signs were a peculiar "fading suntan" complexion and a slightly enlarged and tender liver Diiodo-hydroxyquinoline (diodoquin®), in full adult dosage, is recommended for all children who weigh more than 30 pounds (13.6 Kg)

Nuñez,⁸⁵⁴ in a well illustrated article, emphasizes the following roentgenologic aspects (a) involvement of several segments of the intestinal tract, with a normal appearance between the lesions, (b) less deformity of involved areas than is seen in intestinal tuberculosis or ulcerative colitis, (c) abnormality of the ileocecal valve, and (d) conical appearance of the tip of the cecum White⁸⁵⁵ concludes that changes of maximum intensity occur in this area and that in chronic infection, the cecal alterations are probably irreversible Zucker⁸⁵⁶ describes a deformity which improved greatly after treatment with emetine hydrochloride and with chiniofon

Hepatitis and abscess of the liver are the most common and most important complications⁸⁵⁷ Pleuropulmonary amebiasis occurs in probably 75 per cent of cases as the result of rupture of a hepatic abscess through the diaphragm, in the remainder of cases, it probably results

849 Blumenthal, H. T., Dutra, F. N., Vaschal, H., and Kuhn, L. R. The Significance of *Endamoeba Histolytica* in Stools of Individuals with Acute Diarrhea of Moderate Severity, *Am J Trop Med* **27** 711, 1947

850 Sandler, R. The Symptomatology of Chronic Amebiasis, *Am J Digest Dis* **15** 122, 1948

851 Groff, H. D. Chronic Intestinal Upsets Due to Amebiasis, *Delaware State M J* **20** 116, 1948

852 Miller, M. J. Studies on Amebiasis, *Canad M A J* **57** 373, 1947

853 Loeber, M., and D'Antoni, J. S. Some Recent Experiences with Amebiasis in Children, *New Orleans M & S J* **100** 276, 1948

854 Nuñez, C. J., and Palazzo, D. E. Radiologic Alterations of the Colon in Amebiasis, *Medicina, Buenos Aires* **7** 129, 1947

855 White, R. B. Chronic Amebiasis of the Cecum, *Illinois M J* **93** 102, 1948

856 Zucker, G. Amebic Granuloma of the Cecum, *Rev Gastroenterol* **14** 609, 1947

857 Akenhead, W. R. Extra-Intestinal Amebiasis, *New Orleans M & S J* **100** 105, 1948

from hematogenous spread Amebic abscess of the brain is rare and almost never occurs in the absence of amebic infection of the liver and/or lungs Ulceration and abscess of the skin is a rare complication and usually represents a secondary manifestation of rupture, or drainage of a hepatic or pericolic abscess through the skin Occasional instances of perianal extension of amebic proctitis have been reported Amebic ulceration of the buttocks is described in the case of a patient with cysts in the feces, there were no gastrointestinal symptoms⁸⁵⁸ A death is reported from multiple hepatic and pulmonic abscesses, without involvement of the diaphragm⁸⁵⁹ A patient with cerebral amebiasis recovered after treatment with emetine⁸⁶⁰ Amebic colitis developed after cholecystectomy⁸⁶¹, the patient was treated successfully with emetine Anemia was apparently the only definite clinical manifestation in 1 patient⁸⁶²

The effect of various chemotherapeutic agents on 31 monkeys was studied⁸⁶³ Three trivalent arsenicals were considered of value Carbarsone oxide proved effective in 1 case The possible mechanisms of antiamebic action are discussed

Parmer⁸⁶⁴ found that injection of emetine into rabbits was followed with a relatively high concentration of the drug in the liver for more than a month, whereas the level in the intestine was considerably lower at all times and became undetectable after four days The high concentration of emetine in the liver and the low concentration in the intestine are suggested as the explanation for the efficacy of emetine in amebic disease of the liver and its comparative ineffectiveness in amebic infection of the intestine

After the administration of a single dose of radiochimiofon to each of 7 subjects, it was observed that absorption of the drug occurred regularly, was small in amount (averaging 12.9 per cent of the dose given), and was rapid, with a peak blood level occurring in approxi-

858 Morton, T. C., and Soutar, S. F. Amebic Abscess of the Left Buttock in a Symptomless Cyst Carrier, *Brit. M. J.* **2**:996, 1947

859 Chapman, B. M., Schwartz, H., and Haislip, D. B. Unusual Complications of Amebiasis, *Ann. Int. Med.* **28**:850, 1948

860 Collard, D. P., and Kendall, D. Cerebral Amœbiasis Treated with Emetine, *Lancet* **2**:17, 1947

861 Robertson, K. M. Acute Amœbiasis Complicating Cholecystectomy, *Lancet* **2**:355, 1947

862 Upham, R., and Shookhoff, H. B. Anemia Due to *Endameba histolytica*, *Rev. Gastroenterol.* **14**:613, 1947

863 Anderson, H. H., Johnstone, H. G., and Hanson, E. L. Experimental Chemotherapy of Amebiasis, *Am. J. Trop. Med.* **27**:153, 1947

864 Parmer, L. B. Relative Efficacy of Emetine in Intestinal and Hepatic Amebiasis, *Proc. Soc. Exper. Biol. & Med.* **68**:362, 1948

mately two hours⁸⁶⁵ There was a consistent pattern of urinary excretion, with the bulk of the drug appearing in the first twelve hours and its excretion being virtually complete by forty-eight hours (Chiniofon is partly broken down after absorption, as a progressively greater proportion of iodine is split off from the compound The unabsorbed portion of the drug appears in the feces, from five to seven specimens being required for complete elimination) Blood levels of clinical significance were not attainable with the doses used

Sodium para-aminobenzoic acid was found to relieve symptoms of amebiasis within one or two weeks⁸⁶⁶ In 4 of 5 instances, stools became negative when para-aminobenzoic acid was taken every two hours throughout the day The ideal blood level is considered to be 30 to 60 mg per hundred cubic centimeters

Nix⁸⁶⁷ and Shrapnel⁸⁶⁸ reevaluate the problem of therapy Further observations are presented by Alkan⁸⁶⁹ and by MacFarlane⁸⁷⁰

Klatskin and Friedman⁸⁷¹ noted early evidence of emetine poisoning, other than local reactions, in 85 of 93 cases Generalized weakness, electrocardiographic changes and increased diarrhea were common Other symptoms included drop in blood pressure, precordial pain, dyspnea, tachycardia, dizziness, headache, nausea, vomiting, tenderness, stiffness of extremities, back and neck, and slight paresthesia The authors point out that toxic manifestations are common within the therapeutic range of emetine Reactions may be delayed, therefore, observations should be made for several weeks after the final dose

Diodoquin® is considered useful in the eradication of the cysts of *E. histolytica*, but it is not an effective drug for the treatment of acute or subacute infection⁸⁷²

865 Albright, E C, Tabern, D L, and Gordon, E S The Metabolism of Chiniofon Using Radioactive Iodine, *Am J Trop Med* **27** 553, 1947

866 Dwork, K G The Use of Para-Aminobenzoic Acid in Amebiasis Preliminary Report, *Bull New York Acad Med* **24** 391, 1948

867 Nix, K G An Evaluation of Anti-Amebic Drugs, *New Orleans M & S J* **100** 108, 1948

868 Shrapnel, B C Oral Emetine in the Treatment of Intestinal Amebiasis, *Am J Trop Med* **27** 527, 1947

869 Alkan, W J Amebiasis Diagnostic and Therapeutic Considerations, *J Trop Med* **50** 175, 1947

870 MacFarlane, L R S Unusual Aspects and Therapy in Amebic Dysentery, *J Roy Army M Corps* **89** 256, 1947

871 Klatskin, G, and Friedman, H Emetine Toxicity in Man Studies on the Nature of Early Toxic Manifestations, Their Relation to the Dose Level, and Their Significance in Determining Safe Dosage, *Ann Int Med* **28** 892, 1948

872 Manson-Bahr, P, and Muggleton, W J The Response of Intestinal Amebiasis to Diodoquin Treatment, *J Trop Med* **51** 23, 1948

Penicillin is a valuable adjunct⁸⁷³

Schistosomiasis—Ottolma⁸⁷⁴ describes a technic for the easy and rapid detection of ova. Refinements in diagnosis by the use of rectal biopsy and a grooved rectal scraper are reported by Meeser and his associates⁸⁷⁵. An improved method of sedimentation of *Schistosoma japonicum* and other helminth ova with the use of 10 per cent ethyl alcohol is described⁸⁷⁶. The preparation of the various skin-testing antigens and their stability and interpretation are described by Blair and Ross⁸⁷⁷. Cercariae produce hyaluronidase when incubated with sodium hyaluronate in the cercarial suspension, this may be a mechanism whereby cercariae penetrate the skin of the host⁸⁷⁸.

In tracing the lesions of schistosomiasis japonicum from the early to the advanced stages, the lesions produced experimentally in animals were seen to bear a pronounced similarity to those of the disease in man⁸⁷⁹. When the ovum enters the tissues, an extensive cellular reaction occurs, this consists chiefly of eosinophilic leukocytes, with fewer neutrophilic leukocytes. In some lesions, necrosis of tissue occurs in a fairly wide zone around the ovum. Epithelioid cells appear, and multinucleated giant cells engulf the ovum. The inflammatory cellular response changes to one in which lymphocytes and plasma cells are most numerous. Fibroblastic and capillary proliferation begin early in the peripheral zone, and, as the lesion advances in age, fibrosis predominates. The oldest lesions consist of shrunken, calcified ova, surrounded by more or less dense fibrous tissue, with moderate lymphocytic cellular infiltration. The early lesions represent an unusual and characteristic reaction to the viable ovum, with necrosis and eosinophils, and the later lesions represent a foreign body reaction. No grossly demonstrable lesions of the stomach were found in 7 cases

873 Wright, A. W., and Coombes, A. E. R. Treatment of Amebic Dysentery, *Lancet* **1** 243, 1948

874 Ottolma, C. The Rectoscopic Biopsy by Transparency. A New Diagnostic Method for *Schistosoma Mansoni*, *Am J Trop Med* **27** 603, 1947

875 Meeser, C. V., Ross, W. F., and Blair, D. M. The Diagnosis of Rectal Schistosomiasis, *J Trop Med* **51**:91, 1948

876 Jahnes, W. G., and Hodges, E. P. An Improved Method of Sedimenting *Schistosoma Japonicum* and Other Helminth Ova, *J Parasitol* **33** 483, 1948

877 Blair, D. M., and Ross, W. F. Observations on the Use of Cercarial Antigen in the Diagnosis of Schistosomiasis, *Ann Trop Med* **41** 46, 1948

878 Levine, M. D., Garzoli, R. F., Kuntz, R. E., and Killough, J. H. On the Demonstration of Hyaluronidase in Cercariae of *Schistosoma Mansoni*, *J Parasitol* **34** 158, 1948

879 Bracken, M. M., Bailey, W. R., and Thomas, H. M., Jr. The Lesions of Schistosomiasis Japonica, *Am J Path* **24**:611, 1948

in which patients were examined roentgenologically and gastroscopically⁸⁸⁰

Hayward⁸⁸¹ presumes that although few cases of schistosomiasis haematobia have appeared in New York state, the possibility of such infection is greater than ever before

Seventy-two patients with acute schistosomiasis japonica were treated with antimony potassium tartrate (tartar emetic) intravenously⁸⁸² In 32 cases, degenerated eggs were present in the third and fourth week after the tartar emetic was given, patients in this group were retreated with 40 cc of stibophen N F (fuadin®) Retreatment with stibophen had no effect in the prevention of recurrences The authors state that the patients so treated had fewer recurrences than those in a comparable group, treated with stibophen alone Trivalent antimony compounds, employed in 141 proved cases of schistosomiasis japonica, produced alterations in the T wave of the electrocardiogram, the changes were reversible and were not accompanied with symptoms⁸⁸³ Of 25 patients treated with sodium antimony tartrate, 16 had a two day course and 9, a six day course⁸⁸⁴ The rates of relapse were 31 and 33 per cent All patients who were cured ceased to pass ova by the end of the third week after treatment In 8 cases, the passage of ova persisted, of these patients, 2 received a second course, with disappearance of the ova

APPENDIX

Roentgenologic Examination—The roentgenologic findings in appendicitis, appendical abscess, tuberculosis, diverticulosis and intussusception of the appendix and benign and malignant tumors of the appendix are discussed in detail by Delario⁸⁸⁵

Appendicitis—Bowen⁸⁸⁶ states that spasm of the appendix may lead to obstruction and the formation of stercoliths and, thereby, to the development of appendicitis

880 Palmer, E D Results of Certain Studies on the Stomach in Schistosomiasis Japonica, *Am J Trop Med* **27** 45, 1947

881 Hayward, W G Schistosomiasis, *New York State M J* **48** 796, 1948

882 Carroll, D, and Honninger, A V Studies on Schistosomiasis Japonica in the Philippine Islands, *Bull Johns Hopkins Hosp* **82** 366, 1948

883 Tarr, L Effect of the Antimony Compounds, Fuadin and Tartar Emetic, on the Electrocardiogram of Man A Study of the Changes Encountered in One Hundred and Forty-One Patients Treated for Schistosomiasis, *Ann Int Med* **27** 970, 1947

884 Girgis, B, and Aziz, S Treatment of Schistosomiasis, *Lancet* **1** 206, 1948

885 Delario, A J X-Ray Examinations of the Vermiform Appendix, *Am J Digest Dis* **15** 151, 1948

886 Bowen, W H Spasm as a Factor in Appendicitis, *Brit J Surg* **35** 89, 1947

Sehested and Hein⁸⁸⁷ describe a maneuver in which the examiner sits or stands behind the patient, who is leaning forward, and gives a sharp blow over the costovertebral angle on each side. Pain was produced over McBurney's point in 84 of 85 cases of appendicitis. In other acute abdominal diseases, "indirect percussion" produced pain over the organ involved.

Calvey⁸⁸⁸ postulates a relation between epidemic respiratory infection and acute appendicitis.

Schlicke and Harper⁸⁸⁹ emphasize the fact that parasitic infections and dysentery may simulate appendicitis.

Appendical calculi, recognizable roentgenologically, tend to cause acute appendicitis, with perforation in about 50 per cent of cases⁸⁹⁰

Among 1,487 children below the age of 14, treated for acute appendicitis, 42 were under the age of 3, 8 deaths occurred in the latter group⁸⁹¹. Acute appendicitis with perforation is reported in a 12 month old child⁸⁹².

Meiling⁸⁹³ reviews the problem of appendicitis during pregnancy. The optimum treatment during the first seven and one-half months of pregnancy is careful appendectomy, the decision for operation in the last two and one-half months is more difficult. Cesarean section with low transverse laparotracheotomy is suggested, followed with appendectomy, intraperitoneal implantation of 5 to 10 Gm of sulfanilamide, massive doses of penicillin and the usual nutritional care.

In cases in elderly people, the symptoms are usually masked and indefinite⁸⁹⁴. The process in 1 case was ascribed to the presence of metallic mercury, introduced accidentally by rupture of the balloon.

887 Sehested, N. A., and Hein, J. Indirect "Blow" Percussion in Acute Appendicitis, *Nord med* **37** 188, 1948.

888 Calvey, G. L. Appendicitis and Upper Respiratory Infection. A Report of Eighteen Cases at Sea, *Ann Int Med* **28**:998, 1948.

889 Schlicke, C. P., and Harper, S. B. Diagnosis of Acute Appendicitis in the Tropics, *Am J Surg* **75** 582, 1948.

890 Felson, B., and Bernhard, M. The Roentgenologic Diagnosis of Appendiceal Calculi, *Radiology* **49** 178, 1947. Childe, A. E. Calcified Appendiceal Fecal Concretions in Childhood, *Am J Roentgenol* **58** 455, 1947. Thomas, S. F. Appendical Coproliths. Their Surgical Importance, *Radiology* **49** 39, 1947.

891 Williams, H. Appendicitis in the Young Child, *Brit M J* **2** 730, 1947.

892 Kellert, E., and Dumouchel, A. Appendicitis in Infancy, *Arch Pediat* **65** 194, 1948.

893 Meiling, R. L. Appendicitis Complicating Pregnancy, Labor and the Puerperium, *Surg, Gynec & Obst* **85** 512, 1947.

894 Lamson, S. F. Acute Appendicitis After Middle Life, *Northwest Med* **47** 279, 1948.

of a Miller-Abbott tube⁸⁹⁵ Acute appendicitis accompanied with a large appendicular fecalith and paralytic ileus simulated gallstone ileus clinically and roentgenographically⁸⁹⁶ Acute appendicitis with gangrene developed in a boy of 14, the mass involving the sigmoid colon and producing obstruction⁸⁹⁷

Blanton and Kirk⁸⁹⁸ found that of 61 patients undergoing appendectomy, 51 per cent had either no significant anxiety or an anxiety which subsided with relief from pain and successful postoperative convalescence, 49 per cent had a neurotic reaction

Ligation of the appendix in 10 rabbits resulted in a mortality of 90 per cent within forty hours⁸⁹⁹ A single injection into the ligated appendix of 25,000 to 100,000 units of streptomycin led to 100 per cent survival The intramuscular administration of 400,000 units, in divided doses, resulted in 90 per cent survival Hierton⁹⁰⁰ reemphasizes the importance of maintaining fluid balance and of the liberal use of blood transfusions, in addition to sulfonamide drugs and penicillin, in the treatment of peritonitis

The decrease in mortality from acute appendicitis in the past thirty years is attributed to careful choice of anesthesia, improved technical skill and better postoperative care⁹⁰¹ The continued reduction in mortality from perforated appendix since 1936 is ascribed to intestinal decompression, proper fluid and electrolyte balance, administration of transfusions and of antibiotic drugs, and conservative treatment of those patients in whom perforation has obviously occurred⁹⁰² The value of penicillin is stressed by McCullough⁹⁰³

895 Birnbaum, W Inflammation of the Vermiform Appendix by Metallic Mercury, *Am J Surg* **74** 494, 1947

896 Maloney, G E Acute Appendicitis Simulating Gall-Stone Ileus, *Brit. J Surg* **35** 212, 1947

897 Leggett, L H Acute Appendicitis with Gangrene of the Sigmoid Colon, *Canad M A J* **57** 62, 1947

898 Blanton, S, and Kirk, V A Psychiatric Study of Sixty-One Appendectomy Cases, *Ann Surg* **126** 305, 1947

899 Farris, J M, and Romack, H H The Effect of Streptomycin in "Closed-Loop" Appendicitis, *Surgery* **22** 305, 1947

900 Hierton, T Septic Appendical Peritonitis and Fluid Balance, *Acta chir Scandinav* **96** 224, 1947

901 Schullinger, R N Observations on Mortality from Acute Appendicitis at a University Hospital, 1916 to 1946, *Ann Surg* **126** 448, 1947

902 Schulz, I Perforated Appendix in Children, *Arch Surg* **56** 117 (Jan) 1948

903 McCullough, J Y Survey of Some Aspects of Appendicitis, *Am J Surg* **75** 453, 1948

The mortality rates in different areas over the years have been variable, with numerous factors involved⁹⁰⁴

Intussusception—A cecoileocolic intussusception developed after appendectomy⁹⁰⁵ Intussusception of the appendix is reported⁹⁰⁶

Mucocele—Mucocele of the appendix is rare, and its diagnosis is difficult, usually being made at operation Recurrent pain and the presence of a palpable mass in the right lower abdominal quadrant are highly suggestive⁹⁰⁷ Repetto and others⁹⁰⁸ add 2 cases to 29 previously reported in the Latin American literature Mucocele was associated with myxoglobulosis and intussusception⁹⁰⁹

Diverticula—Diverticulosis of the appendix is described by Maissa⁹¹⁰

Tumors—A pedunculated adenoma was present in a case of intussusception of the appendix into the cecum⁹¹¹ Carcinoid tumors of the appendix are described by Herrera,⁹¹² Chigot, Busser and Bloch-Lainé,⁹¹³ and Crausse and his associates⁹¹⁴

904 Strohl, E L, and Sarver, F E Acute Appendicitis Analysis of Eight Hundred and Seventy-Eight Cases at St Luke's Hospital, Chicago, Arch Surg 55 530 (Nov) 1947 Robbins, F R Appendicitis in a United States Naval Hospital, U S Nav M Bull 47 634, 1947 Molony, J B de W Mortality from Appendicitis in Scotland, 1901-1945, Edinburgh M J 55 153, 1948 Ekstrom, T Appendicitis Material at the Karolinska Sjukhuset 1940-1944, Acta chir Scandinav 96 62, 1947 Gray, T Treatment of Acute Appendicitis, Lancet 2 469, 1947

905 Holm, C Intussusception as a Complication After Appendectomy, Acta chir Scandinav 96 308, 1948

906 Puestow, C B, and Looby, W E Intussusception of the Appendix, Arch Surg 56 544 (April) 1948

907 Kirby, F J Mucocele of the Appendix, Rev Gastroenterol 14 553, 1947

908 Repetto, R L, Bolo, P O, and Jurado, P El mucocele apendicular con estudio de dos casos diagnosticados radiológicamente, Medicina, Buenos Aires 7 315, 1947

909 Probst, J G, and Lassar, G N Mucocele of the Appendix with Myxoglobulosis, Ann Surg 127 171, 1948

910 Maissa, P A Diverticulosis del apéndice, Prensa méd argent 34.1710, 1947

911 Brewer, A C, and Marcus, R Adenomatous Appendicular Polyp Causing Intussusception, Brit J Surg 35 434, 1948

912 Herrera, J M A Case of Carcinoid Tumor of the Appendix, Arch Hosp Santo Tomas 2 185, 1947

913 Chigot, Busser, and Bloch-Lainé Tumeurs endocrines de l'appendice et appendicite aigue, Arch d mal de l'app digestif 36 497, 1947

914 Crausse, Stoupe, Thiebaut, and Vandiest, L Les carcinoids de l'appendice, Acta gastroenterol belg 11 35, 1948

COLON

Physiologic Studies—The response of the exteriorized mucosa to the local application of sympathomimetic and parasympathomimetic drugs was studied by Shoshkes⁹¹⁵ in cases in which colostomy was performed. Epinephrine U S P (adrenalin[®]) and ephedrine were found to be the most effective of the sympathomimetic drugs used, pilocarpine hydrochloride and physostigmine salicylate (eserine) were the most effective of the parasympathomimetic group. The reaction of the colonic mucosa varied greatly, both qualitatively and quantitatively.

Conjugated bile acids, desoxycholic and cholic acid, choline and the choline salts of these bile acids exert analogous influences on the isolated small and large intestine of the guinea pig when applied to the internal surface⁹¹⁶. Small doses always cause stimulation of the rhythmic movements. With larger doses, the tonus increases and tends to counteract the wave movements, this is expressed by slowing of the rate and, later, by decreasing amplitude of the waves. Bile acids tend to stimulate the oscillatory movements, choline has a stronger influence on tonus.

The administration of diisopropyl fluorophosphate, a potent anticholinesterase drug, to human subjects caused a pronounced increase in motility for two to five hours⁹¹⁷. The effect was inhibited temporarily with atropine, morphine or meperidine hydrochloride (demerol hydrochloride[®]) and increased temporarily with neostigmine. It is thought that diisopropyl fluorophosphate irreversibly inactivates cholinesterase, which is regenerated slowly.

Anatomic Studies—According to Duran-Jorda,⁹¹⁸ the small intestine, the colon and the rectum contain a semisquamous epithelial layer, which joins the stratum corneum of the anal skin. It is regarded as similar to the layer in the gastric mucosa and contains an important network of capillaries. The vascularity of the colon has been restudied by Bertocchi⁹¹⁹.

915 Shoshkes, M. Response of the Colonic Mucosa to the Local Application of Sympathomimetic and Parasympathomimetic Drugs, *Gastroenterology* **10** 305, 1948.

916 Meyer, A. E., and McEwen, J. P. Bile Acids and Their Choline Salts Applied to the Inner Surface of the Isolated Colon and Ileum of the Guinea Pig, *Am J Physiol* **153** 386, 1948.

917 Grob, D., Lilienthal, J. L., Jr., and Harvey, A. M. The Administration of Di-Isopropyl Fluorophosphate (DFP) to Man, *Bull Johns Hopkins Hosp* **81** 245, 1947.

918 Duran-Jorda, F. Histopathology of the Semisquamous Epithelial Layer in the Colon, *Rev Gastroenterol* **14** 595, 1947.

919 Bertocchi, A. Contributo allo studio della vascolarizzazione del colon. Le arcate anastomotiche, *Chirurgia* **2** 193, 1947.

Gas—Pogrud and Steggerda⁹²⁰ point out that the absorption rate of gas depends on the partial pressure gradient existing between the lumen of the bowel and the venous blood. The high blood tension of nitrogen (approximately 80 volumes per cent or 608 mm of mercury) retards its absorption from the colon. The beneficial effect of oxygen inhalation on abdominal distention is explained by the removal of nitrogen from the blood, thereby producing a partial pressure gradient favorable for the absorption of nitrogen from the gastrointestinal tract.

Of the measures available for increasing the output of flatus, posterior pituitary injection U S P (solution pituitrin®), given intramuscularly, is the most valuable⁹²¹. It is reassuring to learn that the amount and composition of flatus do not differ in normal persons receiving lactose and those receiving cow's milk⁹²².

Laxative—Sodium carboxymethylcellulose, a new synthetic colloid laxative, gave results in the cases of 109 of 128 patients which were interpreted as good, or better than those obtained with formerly used laxatives, no untoward reactions were noted⁹²³.

Output of Fat and Nitrogen—Wollaeger and others⁹²⁴ measured the total solids, fat and nitrogen in the feces of 11 healthy adult subjects given an identical test diet.

In spite of the completely uniform dietary intake, the various fecal components varied considerably. The total fecal solids varied from 13.6 to 39.1 Gm and averaged 27.6 ± 2.2 Gm per day. The fecal fat (ether-soluble fraction) varied from 1.8 to 6.7 Gm and averaged 4.1 ± 0.5 per day. The fecal nitrogen varied from 0.8 to 2.5 Gm and averaged 1.7 ± 0.1 Gm per day.

Comparison of the values obtained during the use of this test diet with those obtained when a high fat diet was employed disclosed that

920 Pogrud, R. S., and Steggerda, F. R. Studies on Removal of Gas from Colon by Oxygen Inhalation, *J Aviation Med* **19** 204, 1948, The Influence of Gaseous Transfer Between the Colon and Blood Stream on Percentage Gas Compositions of Intestinal Flatus in Man, *Am J Physiol* **153** 475, 1948.

921 Alstead, S., and Patterson, J. F. Assessment of Intestinal Carminatives, *Lancet* **1** 437, 1948.

922 Kirk, E., and Møller, A. V. Investigations on the Amount and Composition of Flatus in Normal Individuals Before and After Ingestion of Lactose and Cow's Milk, *Acta med Scandinav* (supp 206) **130** 488, 1948.

923 Fittipaldi, J., and Davis, P. L. Sodium Carboxymethylcellulose Laxative Effects in Clinical Use, *Gastroenterology* **10** 667, 1948.

924 Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E. Total Solids, Fat and Nitrogen in the Feces. III. A Study of Normal Persons Taking a Test Diet Containing a Moderate Amount of Fat, Comparison with Results Obtained with Normal Persons Taking a Test Diet Containing a Large Amount of Fat, *Gastroenterology* **9** 272, 1947.

the values for fecal total solids, nitrogen and percentage of ingested fat in the stool were remarkably similar. The weight of fecal fat and the percentage of fecal solids that were fat were greater with the larger than with the smaller fat intake. The authors conclude that the quantity of fat in the feces of normal human beings is considerably influenced by the amount of fat ingested. This factor suggests that unabsorbed fat may account for a larger proportion of the fecal fat than is commonly supposed.

Roentgenologic Examination—If the urinary bladder is filled with 200 to 400 cc of sodium chloride solution or water, the bladder pushes the sigmoid from the true pelvis, producing unfolding of the loops, with separation from the rectosigmoid. Roentgenologic examination of the sigmoid with a full urinary bladder is recommended for this reason.⁹²⁵ The value of the roentgenologic examination in the diagnosis of lesions beyond the reach of the sigmoidoscope⁹²⁶ and the importance of repeated examination in the presence of suspicious clinical findings⁹²⁷ are reaffirmed.

Proctosigmoidoscopy—Among 1,000 cases in which routine proctosigmoidoscopic examinations were performed, abnormalities were found in 30.6 per cent, significant pathologic features were observed in 5.5 per cent of 200 cases in which examinations were performed without definite indication, and in 84 per cent of 200 cases in which examinations appeared indicated on the basis of clinical findings.⁹²⁸ Schapiro⁹²⁹ discusses the procedure as it applies to infants and children.

Andresen⁹³⁰ analyzed 46 reports of perforation of the rectosigmoid by the proctoscope, collected by questionnaires, and compared them with 48 reports of perforation previously described in the literature. In the 94 cases, approximately one-half the patients died. The mortality from immediate operation, however, decreased during the ten years previous to the time of writing. Spontaneous recovery in 9 cases in which the patient was not operated on suggested that many more patients might

925 Fletcher, G. H. An Improved Method of Visualization of the Sigmoid, *Am J Roentgenol* **59** 750, 1948.

926 Green, W. E. Evaluation of the Roentgenologic Diagnosis of Lesions of the Rectum and Sigmoid, *Am J Surg* **75** 348, 1948.

927 Maxfield, J. R. Radiologic Diagnosis of Lesions of the Large Bowel, *Texas State J Med* **43** 276, 1947.

928 Browne, D. C., and McHardy, G. An Evaluation of Routine Proctosigmoidoscopy, *South M J* **41** 372, 1948.

929 Schapiro, S. Applied Anatomy of Infants and Children in Proctology, *Rev Gastroenterol* **15** 307, 1948, *The Proctologic Examination of Infants and Children*, *J Pediat* **32** 543, 1948.

930 Andresen, A. F. R. Perforations from Proctoscopy, *Gastroenterol* **9** 32, 1947.

do better without operation. Rupture of the rectosigmoid during sigmoidoscopy in the case of a woman⁹³¹ with advanced hypertensive cardiovascular-renal disease, examined because of rectal bleeding, resulted in death six days later, the pathologic diagnoses were hypertensive cardiovascular-renal disease with myocardial failure, multiple venous thromboses and perforation of the sigmoid, with pelvic abscess.

Volvulus—Seven cases of volvulus of the cecum and the ascending colon are presented⁹³². All patients but 1 were in the middle or elderly age group, 2 had had more than one previous attack, 4 were able to expel flatus or defecate in spite of the volvulus. At operation, the most frequent location of the cecum was noted to be in the left upper quadrant. The only death occurred in the case of a patient treated by resection and primary ileotransverse colostomy. The treatment is surgical, if there is the slightest question of the viability of the cecum, a Mikulicz resection and exteriorization should be done. An interesting case of volvulus of the cecum is reported in a woman of 76⁹³³. The findings were characterized by great distention of the cecum and the ascending colon in the left half of the abdomen and by the absence of a cecal shadow, on roentgenologic examination, in the right lower quadrant. The diagnostic value of the roentgenologic examination is emphasized by Olivier⁹³⁴ and by Christiaens⁹³⁵. The only treatment required in most cases of volvulus of the sigmoid, according to Brunsgaard,⁹³⁶ is proctoscopy and intubation. Although torsion of the sigmoid usually causes obstruction of the lumen, strangulation and circulatory disturbance of the involved segment are seldom present when the patient is hospitalized. If attempts at intubation fail, detorsion is accomplished through an abdominal incision, resection is reserved for cases with gangrene. This conservative regimen, used in the treatment of 91 patients, reduced the mortality rate from the 30 to 60 per cent accompanying operative treatment to a low of 14 per cent. Rea⁹³⁷ expresses similar opinions.

931 Pfeiffer, M. C. J. Rupture of Rectosigmoid During Sigmoidoscopy, *Am J Surg* **75** 281, 1948.

932 Young, E. L., Morrison, H. R., and Wilson, W. E., Jr. Volvulus of the Cecum and Ascending Colon, *New England J Med* **237** 78, 1947.

933 Gibson, R. H., and Musgrove, J. E. Volvulus of the Cecum, *Proc Staff Meet, Mayo Clin* **23** 260, 1948.

934 Olivier, C. Radiographie du volvulus sigmoïdien, *Presse méd* **56** 352, 1948.

935 Christiaens, J. Le volvulus chronique du caeco-colon, *J belge de radiol* **30** 230, 1947.

936 Brunsgaard, C. Volvulus of the Sigmoid Colon and Its Treatment, *Surgery* **22** 466, 1947.

937 Rea, C. E. Experiences in the Treatment of Volvulus of the Sigmoid, *Minnesota Med* **31** 653, 1948.

Gilchrist⁹³⁸ discusses the diagnostic and therapeutic aspects in 4 cases of acute obstruction produced by volvulus of the sigmoid and in 1 in which obstruction was caused by volvulus of the cecum. In acute obstruction due to volvulus of the cecum, there is an early associated obstruction of the small bowel, the patient is sicker than if he had a similar lesion in the sigmoid. Early operation is indicated, untwisting, with fixation to the bottom of the pelvis and the left pelvic wall, is the safest procedure. If the bowel is gangrenous, resection and anastomosis between the ileum and the transverse colon are indicated. If the untwisting and fixation fail to give permanent relief, resection of the redundant bowel with lateral anastomosis is indicated. Six cases of volvulus of the sigmoid are described by Woronov and his associates⁹³⁹.

Diverticulosis and Diverticulitis—The subject is discussed generally by a number of authors⁹⁴⁰.

Anderson⁹⁴¹ reviews 99 cases in which operation was performed for diverticulitis of the cecum. The average age was less than 40, the sexes were equally represented. Appendicitis was the preoperative diagnosis in 84 per cent of cases. Similar cases are reported by Fairbank and Rob⁹⁴² and by Zuckerman and Altman⁹⁴³. A large diverticulum of the cecum simulated a tumor⁹⁴⁴.

Among 200 patients with diverticulitis, one fifth had lumbosacral pain⁹⁴⁵. Other common symptoms included change in bowel habits,

938 Gilchrist, R. K. Obstruction Due to Volvulus of the Colon, *Arch Surg* **56** 79 (Jan) 1948.

939 Woronov, V. D., Epstein, B. S., and Louria, H. W. Volvulus of the Sigmoid Colon, *New York State J Med* **48** 1364, 1948.

940 Gerwig, W. H. Diverticula and Other Mucosal-Lined and Pathological Out-Pouchings of the Gastrointestinal Tract, *Am J Surg* **74** 462, 1947. Scott, H. G. Alimentary Diverticula, *Minnesota Med* **30** 1284, 1947. Stalker, L. K., and Wittmer, S. C. Diverticulosis and Diverticulitis of Colon, *New York State J Med* **47** 1693, 1947. Boyd, J. T. Diverticulosis and Diverticulitis, *Texas State J Med* **43** 681, 1948. Kellogg, W. A. Diverticulosis of the Gastrointestinal Tract, *Ann West Med & Surg* **2** 256, 1948. Centeno, A. M. Diverticulosis del intestino delgado, *Prensa med argent* **34** 1706, 1947. Sabeti, A. M. A Clinical Review of Diverticulitis of the Colon, *J Mt Sinai Hosp* **15** 1, 1948.

941 Anderson, L. Acute Diverticulitis of the Cecum, *Surgery* **22** 479, 1947.

942 Fairbank, T. J., and Rob, C. G. Solitary Diverticulitis of the Cecum and Ascending Colon, *Brit J Surg* **35** 105, 1947.

943 Zuckerman, I. C., and Altman, L. S. Solitary Diverticulum of the Cecum, *New York State J Med* **48** 1398, 1948.

944 Nocito, F. J., and Cottini, G. F. Diverticulo solitario del ciego a forma pseudo-tumoral, *Rev Asoc med argent* **62** 44, 1948.

945 LeRoyer, C. P., and White, B. V. Diagnostic and Therapeutic Problems in Diverticulitis, *New England J Med* **237** 239, 1948.

cramping lower abdominal pain with localized tenderness, fever and increased leukocyte count (exceeding 11,000 cells per cubic millimeter) Melena appeared in more than 16 per cent of the cases Complications occurring in 25 per cent included perforation with abscess formation, mechanical obstruction and peritonitis with ileus and fistula formation

Lesions of the sigmoid may produce symptoms and signs in the right side of the abdomen⁹⁴⁶ Of the conditions in 18 cases reported as demonstrating this fact, 13 were diverticulitis and 5, carcinoma The author points out that the sigmoid should be inspected carefully when, at operation for acute appendicitis, insufficient cause for the clinical symptoms is found in the right iliac fossa

Two fatal cases are reported in which the presenting manifestation was emphysematous cellulitis of the leg⁹⁴⁷ Diverticulitis is the commonest cause of sigmoidovesical fistula⁹⁴⁸

Allen and Donaldson,⁹⁴⁹ on the basis of 59 cases recorded by a gynecologist, call attention to diverticulitis as a frequent cause of pain in the left lower abdominal quadrant, of irritation of the bladder and of a pelvic mass The clinical features, treatment and special problems of diverticulitis, as encountered in women, are discussed in an excellent article by Counseller⁹⁵⁰

The complications of perforation, obstruction and fistula in cases of sigmoid diverticulitis usually require operation⁹⁵¹ Surgical exploration and, frequently, resection of the involved segment of the colon are indicated at times because of the impossibility of distinguishing between carcinoma and diverticulitis The establishment of a colonic stoma proximal to the lesion was associated with hospital mortality rates of 51 per cent in the era before chemotherapy and of 11 per cent in those cases in which chemotherapy was administered The safest plan of treatment proved to be establishment of a stoma proximal to the lesion, followed, after an interval of six to twelve months, with exteriorized resection of the involved bowel Resections of this type were associated with no deaths after chemotherapy became available

946 Lyons, A S The Sigmoid as a Source of Right Sided Symptoms, *Ann Surg* **127** 398, 1948

947 Dawson, R L G, and Hardy, R H Diverticulitis Presenting as Emphysematous Cellulitis of the Leg, *Brit M J* **1** 498, 1948

948 Leigh, T F Sigmoidovesical Fistula, *Am J Roentgenol* **58** 451, 1947

949 Allen, E, and Donaldson, L B Diverticulitis of the Colon in Gynecology, *West J Surg* **55** 393, 1947

950 Counseller, V S Diverticulitis Symptoms, Complications and Management, Particularly in the Female, *Am J Obst & Gynec* **55** 653, 1948

951 Pemberton, J deJ, Black, B M, and Maino, C R Progress in the Surgical Management of Diverticulitis of the Sigmoid Colon, *Surg, Gynec & Obst* **85** 523, 1947

With the risk of operation so greatly reduced, and in view of the obvious advantage of resection, serious consideration can be given to broadening the indications for surgical treatment of diverticulitis. Martin and Candle⁹⁵² likewise state the belief that more radical one stage resections of the involved segment are now possible.

Megacolon—Canónico and Pilheu⁹⁵³ studied 36 cases of megacolon involving only the sigmoid, 66 per cent of patients were between 30 and 60, there were twice as many males as females. The most frequent symptoms were constipation and obstruction. The frequency of complications suggests that the condition is not to be regarded as merely benign. Obstruction due to volvulus or fecal impaction occurred in 13 cases, in 4 of which emergency operations were required. The barium sulfate enema is the most precise method of diagnosis. Medical treatment was used with advantage in cases of moderate difficulty, surgical treatment is indicated in advanced and in complicated cases, in cases of huge megasigmoids, in cases with repeated episodes of mild intestinal obstruction, and when medical treatment has failed to prevent frequent fecal impactions. There were 4 deaths among 30 patients subjected to operation. Bosworth and others⁹⁵⁴ consider that except in advanced cases demanding heroic emergency measures an intensive medical regimen should first be given a thorough trial.

Two cases of congenital megacolon in infants are reported in which the condition responded favorably to the use of amprotopine phosphate (syntropan®)⁹⁵⁵. Both patients had required operation, at which fecal obstruction was relieved manually. Although clinical improvement apparently coincided with administration of the drug, the roentgenologic appearance of the colon was unchanged. The reviewers have not been favorably impressed with the value of atropine or atropine-like compounds in this condition. Among 127 cases of megacolon, Crismer⁹⁵⁶ found evidence of hypothyroidism in 15 per cent, he regards the administration of thyroid extracts as effective therapy. Megacolon in 7 week and 6 month old infants was treated "successfully" by infiltration of the splanchnic nerves with 3 cc of 0.5 per cent solution of procaine.

952 Martin, J. D., and Candle, R. I. Diverticula of the Colon, *South Surg* **14** 82, 1948.

953 Canónico, A. N., and Pilheu, F. R. Megasigma. Consideraciones clinicas quirurgicas sobre treinta y seis casos, *Presna med argent* **35** 484, 1948.

954 Bosworth, B. M., Stein, H. D., and Lisa, J. R. Modern Management of Megacolon, *Am J Surg* **75** 808, 1948.

955 Robbin, L. Congenital Megacolon in Young Infants and Children, *Arch Pediat* **64** 459, 1947.

956 Crismer, R. La part de la thyroïde dans la pathogénie du dolichocolon, *Acta clin belg* **2** 33, 1947.

hydrochloride U S P (novocain[®])⁹⁵⁷ In 4 cases of megacolon, in which the patients were 6, 7, 12 and 70, a valve was found between the sigmoid colon and the rectum⁹⁵⁸, daily high enemas or administration of liquid petrolatum relieved the symptoms for long periods of time

Treatment in 3 cases of megacolon developing in adult life was by presacral, preaortic and inferior mesenteric neurectomy, respectively⁹⁵⁹ One patient died four years and eight months after operation, the other 2 were alive and well at the time of writing, three years eight months and two years one month respectively, after operation Of 17 patients with congenital megacolon treated by spinal anesthesia during the period from 1938 to 1945 11 were reexamined, a detailed report on the twelfth patient was received⁹⁶⁰ The results were interpreted as good in 8 cases fair in 2, and poor in 2 The method is regarded as purely empiric, but simple and effective Twelve years seems to be the upper age limit for success The procedure is considered useless in the megacolon of adults, which is usually mechanical in origin Sandberg⁹⁶¹ does not recommend neurosurgical therapeutic procedures He states that in his opinion the period of observation for patients so treated has not been sufficiently long He reports the cases of 3 patients who initially obtained good results from lumbar sympathectomy (lasting one to four years) but required resection of the colon later

Various authors⁹⁶² report favorable results after surgical intervention in single cases or in small groups of cases Jenkins⁹⁶³ recommends partial sphincterectomy in all cases of Hirschsprung's disease with probable spasm or hypertrophy of the internal anal sphincter Five

957 Hillemand, P, Duguet, M, and Gautier, P A propos de deux cas de maladie de Hirschsprung, *Arch d mal de l'app digestif* **36** 393, 1947

958 Muskens, A L M Megacolon Congenitum (Valvulaire), *Nederl tijdschr v geneesk* **91** 1616, 1947

959 Smithy, H G, and Kredel, F E Localized Acquired Megacolon Treated by Sympathectomy, *Surgery* **22** 259, 1947

960 Telford, E D, and Haxton, M A Congenital Megacolon Results of Treatment by Spinal Anesthesia, *Brit M J* **1** 827, 1948

961 Sandberg, I R Surgical Treatment of Megacolon, *Nord med* **33** 445, 1947

962 Hojensgard, J C Constipation Caused by Megasigmoid Treated by Sigmoid Resection, *Nord med* **35** 1881, 1947 Hersh, J Congenital Megacolon-Hirschsprung's Disease, *Am J Surg* **74** 815, 1947 Hepp, J, and Petit, P Les difficultes du traitement de la maladie de Hirschsprung Un cas de colectomie totale de necessite, *Arch d mal de l'app digestif* **36** 387, 1947 Arenander, E On the Treatment of Hirschsprung's Disease, with Report of an Operated Case, *Acta chir Scandinav* **96** 123, 1947

963 Jenkins, J A Hirschsprung's Disease, *Australian & New Zealand J Surg* **13** 189, 1948

cases of megacolon are described by a group of French authors⁹⁶⁴ All the patients had been subjected to one or more operative procedures, including sympathectomy, sphincterectomy, cecal colostomy and segmental colectomy None received more than temporary benefit, total colectomy was eventually performed for all

Microcolon—In congenitally small colon, or microcolon, the entire large bowel, except the rectum, of a newborn infant has an anatomic diameter of approximately 4 to 8 mm, there are accompanying hypertrophy and dilatation of a segment of small intestine, usually the ileum⁹⁶⁵

Functional Disorders—The clinical features and treatment of irritable colon are reviewed in a useful article by Collins⁹⁶⁶ Gerendasy⁹⁶⁷ contends that functional disturbances of the gastrointestinal tract may be caused by local anorectal disease, with reflex stimulation of the vegetative nervous system

The lysozyme content of feces was measured in random and twenty-four hour specimens from patients with various types of bowel disorders, healthy persons and persons with diseases other than those primarily involving the colon⁹⁶⁸ In 2 cases of ulcerative colitis, lysozyme values rose after emotional tension In the case of a male physician, lysozyme values increased slightly after his delivering a lecture and suffering with a migraine headache A patient with "mucous colitis" manifested higher lysozyme levels during a period of emotional tension than during a period of calm One female patient with ulcerative colitis showed essentially unchanged lysozyme values during psychotherapy Pre-vagotomy and postvagotomy values in the case of a patient with ulcerative colitis were essentially the same These and other observations are of considerable interest, however, much more data are necessary before the significance of the lysozyme content of the feces can be fully evaluated

964 Mialaret, J Colectomie totale pour megacôlon apres echec d'une resection sigmoïdienne, *Mem Acad de chir* **73** 209, 1947 Hepp, J, and Petit, P Colectomie totale pour maladie de Hirschsprung apres echec d'une double sympathectomie lombaire et d'une hemicolectomie gauche, *ibid* **73** 213, 1947 Boppe Colectomie totale pour megacôlon apres echec d'une colectomie segmentaire, *ibid* **73** 220, 1947 d'Allaines, F Colectomie totale pour mégacôlon, *ibid* **73** 246, 1944

965 Zimmer, J Microcolon, *Acta radiol* **29** 228, 1948

966 Collins, E N The Diagnosis and Treatment of Irritable Colon Physiologic, Local Irritative and Psychosomatic Factors, *M Clin North America*, **32** 398, 1948

967 Gerendasy, J Relationship of Proctologic Diseases to Gastrointestinal Disorders, *Rev Gastroenterol* **14** 492, 1947

968 Grace, W J, Seton, P H, Wolf, S, and Wolff, H G Changes in Lysozyme Formation in the Human Colon in Various Emotional States, *Bull New York Acad Med* **24** 390, 1948

Ulcerative Colitis—Palmer⁹⁶⁹ discusses the pathogenesis and treatment of chronic ulcerative colitis

as a clinical entity of varied etiology, an inflammation of the bowel induced by organisms some of which are known and some unknown. Hypermotility produced in any manner may predispose the mucosa to infection, promote the extension of the infection, increase the inflammation, and thus increase the severity of the disease. The therapeutic approach [is] multiple with attention to the emotional, physiologic and antibiotic possibilities. Surgery is indicated for various complications.

Further observations are contributed by Fradkin⁹⁷⁰

Sixty-one patients with chronic ulcerative colitis were examined five to thirty months after the onset of the disease⁹⁷¹. The initial clinical picture was considered that of acute bacillary dysentery, although bacteriologic data were scarce. The presence of dysentery bacilli was determined in 98 per cent of the cases by aspiration of mucosal crypts. The evidence is interpreted as supporting the thesis that chronic ulcerative colitis and distal ileitis are the result of acute bacillary dysentery. A bacteriologic and immunologic study was carried out by Wagner and Maratka⁹⁷² in 31 cases of ulcerative colitis. Of the organisms obtained by culture, none was strictly pathogenic. Although special efforts were directed to their isolation, dysentery bacilli were not found. The authors conclude that allergy to the existing colonic flora plays an important part in the pathogenesis of the disease, but they cannot decide whether this is the primary cause or whether such a mechanism is superimposed on a more fundamental, and as yet unknown, disturbance.

Rodger⁹⁷³ suggests further study of reflex pathways involved in the production of vasoconstriction of the colon, to clarify the pathogenesis of ulcerative colitis. Baker⁹⁷⁴ suggests that emotional trauma, by stimulating the intestine and producing spasm and hyperperistalsis, alters the mucous secretion, as a result, the mucosa becomes vulnerable to infection.

969 Palmer, W. L. Chronic Ulcerative Colitis, *Gastroenterology* **10** 767, 1948

970 Fradkin, W. E. The Etiologic Diagnosis of Ulcerative Colitis, *Am J Digest Dis* **15** 119, 1948

971 Felsen, J., and Wolarsky, W. Bacillary Dysentery and Chronic Ulcerative Colitis in World War II, *Science* **105** 213, 1947, Bacillary Dysentery and Ulcerative Colitis, *Gastroenterology* **9** 557, 1947

972 Wagner, V., and Maratka, Z. A Contribution to the Bacteriology and Immunology of Ulcerative Colitis, *Gastroenterologia, Bohemia* **1** 41, 1947

973 Rodger, D. E. The Challenge of Colitis, *Canad M A J* **58** 153, 1948

974 Baker, W. Y. Psychologic Aspects of Ulcerative Colitis, *Northwest Med* **47** 271, 1947

Ricketts, Kirsner and Palmer⁹⁷⁵ noted an apparently normal colon on roentgenologic examination in the cases of 60 of 156 patients with typical clinical evidence of nonspecific ulcerative colitis. A roentgenologic study of the course of the disease indicated that the extent of roentgenologic involvement is not correlated with the type of onset, the duration of symptoms or the clinical severity. As noted roentgenologically, regression occurred in approximately 10 per cent and progression in approximately 25 per cent of cases, there was no change in 65 per cent. Variations in the clinical manifestations occurred independently of the roentgenologic appearance of the colon.

An accurate and simple method for the determination of the p_H of feces, utilizing the Beckman p_H meter, is described⁹⁷⁶. The normal p_H of the soft, formed stools of healthy young adults ranges from 6.4 to 7.5, readings for each person showing a maximum deviation of 0.4 units or less from the mean. Loose stools are always acid, hard stools are always alkaline. In the cases of 5 untreated patients with chronic idiopathic ulcerative colitis, the feces were found to be considerably below the normal limits of acidity. The rate of passage of intestinal contents from mouth to anus, as determined by the test with carmine red, bears no relation to the variation in the p_H of normal feces.

According to Crohn, Garlock and Yarnis,⁹⁷⁷ 8 per cent of all cases of nonspecific ulcerative colitis fall into a distinct subgroup, composed of those involving primarily the right colon. The process may affect the terminal ileum or may progress, either continuously or by skipping, to involve the remainder of the colon. Seventy-seven cases of this type are described. Medical management was recommended initially, although it was thought that operation would eventually be required in most. The recommended procedure is ileocolostomy (special care being taken to enter below the involved portion of the colon), with exteriorization of the proximal portion of the colon and, later, resection of the diseased portion. The prognosis is good.

Ross and Swarts⁹⁷⁸ describe 2 cases of hepatic disease associated with ulcerative colitis. A man of 22 who died of hepatic failure was thought to have primary disease of the liver (toxic cirrhosis), noninflam-

975 Ricketts, W. E., Kirsner, J. B., and Palmer, W. L. Chronic Non-Specific Ulcerative Colitis, *Gastroenterology* **10** 1, 1948.

976 Shoshkes, M. The Hydrogen Ion Concentration of the Feces, *Gastroenterology* **9** 765, 1947.

977 Crohn, B. B., Garlock, J. H., and Yarnis, H. Right-Sided (Regional) Colitis, *J. A. M. A.* **134** 334 (May 24) 1947.

978 Ross, J. R., and Swarts, J. M. Hepatic Dysfunction and Cirrhosis in Chronic Ulcerative Colitis, *Gastroenterology* **10** 81, 1948.

matory in origin. The other patient, a woman of 28, who survives, was thought to have inflammatory hepatobiliary disease. Twenty cases of active ulcerative colitis were studied by various laboratory procedures, in no instance did the pattern of hepatic function tests per se justify a diagnosis of latent disease of the liver. One hundred and fifty unselected cases of chronic ulcerative colitis were reviewed to determine the number with gross clinical evidence of liver disease, none was found. Autopsy findings in 27 cases of chronic ulcerative colitis were analyzed to determine the degree of significant hepatic disease and were compared with findings in 100 unselected cases, in which death occurred from other causes. The authors state: "There was no greater incidence of hepatic insufficiency than occurs in other maladies where uncorrected factors of severe anemia, marked weight loss, and/or negative nitrogen balance appear." The authors conclude that correction of malnutrition, protein deficit and severe anemia are not only necessary in the treatment of ulcerative colitis per se but offer needed protection to a laboring liver. In another article, Ross⁹⁷⁹ reports on the relation of hepatic insufficiency to chronic ulcerative colitis.

Lyons and Postlethwait⁹⁸⁰ report ulcerative colitis, confirmed pathologically, in male twins. The disease developed in 1 at the age of 17 and in the other at the age of 20. In the case of a woman with ulcerative colitis of twelve years' duration, pyoderma developed after ileostomy and subsided after colectomy.⁹⁸¹ Gallagher⁹⁸² describes an interesting case of regional colitis, involving the rectosigmoid area. *Proteus morganii* was isolated from the stool of a patient with hemorrhagic colitis, complicated by perforation.⁹⁸³ Collins and Bynum⁹⁸⁴ report an interesting case of severe ulcerative colitis in a veteran of 27. Roentgenograms disclosed extensive ulcerative colitis involving the entire colon and rectum with suggestive pseudopolypoid changes. Numerous examinations of warm stools failed to reveal parasites, indeed, no specific etiologic factor could be demonstrated. However, dramatic improvement

979 Ross, J. R. The Relationship of Hepatic Insufficiency to Chronic Ulcerative Colitis, *S. Clin. North America* **28** 701, 1948.

980 Lyons, C. K., and Postlethwait, R. W. Chronic Ulcerative Colitis in Twins. Case Report, *Gastroenterology* **10** 545, 1948.

981 Corbett, R. S. Specimen of Colon Removed on Account of Severe Pyoderma from a Longstanding Case of Chronic Ulcerative Colitis, *Proc. Roy. Soc. Med.* **40** 871, 1947.

982 Gallagher, F. T. Rectosigmoiditis. A Non-Specific Stenosing Entity, *Ohio State M. J.* **43** 1148, 1947.

983 Paris, J., and Tacquet, A. Infection mortelle a bacille de Morgan. Pneumo-peritoine spontané par perforation occulte, *Presse med.* **19** 222, 1947.

984 Collins, E. N., and Bynum, F. L. Amebiasis and Indeterminate Ulcerative Colitis, *M. Clin. North America* **32** 408, 1948.

occurred after treatment with emetine, subsequently, the roentgenologic findings indicated a normal colon. In 100 consecutive cases of amebiasis recorded at the Cleveland Clinic, only 11 patients had acute dysenteric symptoms. The authors suggest an initial course of antiamebic therapy in cases of apparently undetermined ulcerative colitis, even though *Endamoeba histolytica* is not demonstrable. The reviewers have encountered numerous patients with ulcerative colitis who had been previously treated unsuccessfully with emetine and other antiamebic drugs.

Smith⁹⁸⁵ reviews the complications of chronic ulcerative colitis, as well as of other ulcerative diseases of the bowel. Carcinoma of the colon is described in 2 cases, in which the patients were 32 and 43, respectively, three separate carcinomas were present in 1 case.⁹⁸⁶

The medical management of ulcerative colitis is reviewed by several authors.⁹⁸⁷ Kirshen^{987b} states that the results of medical therapy have improved remarkably in the past decade. Surgical measures should never be attempted during the acute or fulminating stage, ileostomy should be followed with colectomy.

Kiefer⁹⁸⁸ analyzes the results of medical treatment in a series of 400 cases, 99 patients eventually were operated on, 72 other patients underwent surgical intervention after only a few days' evaluation and preparation. Diplostreptococcus vaccine and antiserum were ineffective. Chemotherapy is not curative and probably has no direct effect on the colitis per se, although in some cases it appears to have some value. Indifferent results were obtained with fever therapy, penicillin therapy and antiamebic and antiallergic therapy. The analysis is interpreted as indicating that ulcerative colitis is both a medical and a surgical disease. Present methods of medical treatment may be adequate in the majority of milder cases. In properly selected cases, surgical intervention is regarded as the most effective and most reliable approach.

Heazlett⁹⁸⁹ administered an autogenous vaccine made from staphylococci isolated from the feces or colonic ulcers of 7 patients, apparent clinical recovery or satisfactory improvement was noted in all.

985 Smith, N. D. Complications Peculiar to Ulcerative Diseases of the Colon, *New York State J. Med.* **47** 2304, 1947.

986 Johnson, T. M., and Orr, T. G. Carcinoma of the Colon Secondary to Chronic Ulcerative Colitis, *Am. J. Digest. Dis.* **15** 21, 1948.

987 (a) Bowman, P. G. Medical Therapy in Ulcerative Colitis, *Minnesota Med.* **30** 956, 1947. (b) Kirshen, M. Ulcerative Colitis. An Evaluation of Etiology, Symptomatology and Therapy, *Am. J. Digest. Dis.* **14** 384, 1947. (c) Speir, E. B. Ulcerative Colitis, *Northwest Med.* **47** 266, 1948. (d) Voegtlin, W. L. Treatment of Ulcerative Colitis, *ibid.* **47** 267, 1948.

988 Kiefer, E. D. An Evaluation of the Clinical Management of Chronic Ulcerative Colitis, *Gastroenterology* **10** 16, 1948.

989 Heazlett, W. E. Treatment of Ulcerative Colitis with Staphylococcus Autovaccine. A Preliminary Report, *Gastroenterology* **10** 634, 1948.

Machella and Miller⁹⁹⁰ studied the effects of alimentation by intubating the bowel to a point just proximal to the diseased area with a Miller-Abbott tube and maintaining constant suction, to prevent the content of the small intestine from entering the diseased area. The procedure allowed temporary rest of the colon ("a medical ileostomy"). Food consisted of an orally administered mixture of enzymatic casein digest and dextrin-maltose,[®] given for varying periods of time, with additional essential vitamins and iron. A remission was induced in 11 of 12 cases, a relapse occurred in 2 of these, but a remission was again induced.

Block and Pollard⁹⁹¹ regard sulfonamide drugs as a valuable adjunct. Penicillin is generally ineffective in inducing remissions but may be valuable in acute febrile complications. Streptomycin has not yet been fully evaluated but may be life saving in controlling fever and toxicity during acute exacerbations. Salazopyrine, an azo compound of salicylic acid and sulfapyridine, was used with "good results" in most cases, however, relapses occurred frequently⁹⁹². Promising results are reported with phthalylsulphathiazole⁹⁹³. Cluer⁹⁹⁴ records 3 cases of "granular proctitis" in which succinylsulphathiazole suppositories were used, with apparently good results.

Daniels,⁹⁹⁵ in discussing the psychiatric aspects, emphasizes two objectives in treatment. The first is to relieve the emotional pressure, discharging through the gastrointestinal tract by allowing the patient to unburden his conflicts verbally ("emotional catharsis"), the second is to promote a better equilibrium with the environment. Ulcerative colitis is considered to fit into present concepts of psychosomatic disease and to present a striking example, because of the often apparent personality immaturity, the previous evidence of neurosis and the clear-

990 Machella, T. E., and Miller, T. Treatment of Idiopathic Ulcerative Colitis by Means of a Medical Ileostomy and an Orally Administered Protein Hydrolysate-Dextrin-maltose Mixture, *Gastroenterology* **10** 28, 1948.

991 Block, M., and Pollard, M. Chemotherapy and Antibiotics in Chronic Ulcerative Colitis, *Gastroenterology* **10** 46, 1948.

992 Svartz, N. The Treatment of One Hundred and Twenty-Four Cases of Ulcerative Colitis with Salazopyrine and Attempts of Desensibilization in Cases of Hypersensitiveness to Sulfa, *Acta med Scandinav* (supp 206) **130** 465, 1948.

993 Trier, E. Treatment of Ulcerative Colitis with Phthalylsulphathiazole, *Acta med Scandinav* (supp 206) **130** 473, 1948.

994 Cluer, E. H. Granular Proctitis Treated with Succinylsulphathiazole Suppositories, *Lancet* **2** 168, 1947.

995 Daniels, E. G. Psychiatric Factors in Ulcerative Colitis, *Gastroenterology* **10** 59, 1948.

cut relation between the precipitating situation and the outbreak of the disease. It has proved to be amenable to psychotherapy when other treatments have failed. Ross⁹⁹⁶ reflects further on this aspect of the problem.

In a case of severe ulcerative colitis, in which the condition was not improved by other methods, a prolonged remission was attributed to propylthiouracil⁹⁹⁷. Ehrlich⁹⁹⁸ presumes that the intestinal mucosa contains "an antiproteolytic substance" whose function is to protect the mucosa from autolysis by the proteolytic enzymes of the intestinal contents. On the basis of this theory, desiccated extract of hog stomach, in doses of 30 to 60 Gm daily, was administered to 15 patients with ulcerative colitis, with apparent improvement. Four patients required sulfonamide therapy for secondary infection. Four patients relapsed and required a second course of therapy. The reviewers maintain a conservative attitude toward these various therapeutic measures and wish to emphasize the importance of careful, prolonged and well controlled study, keeping ever in mind the "spontaneous" remissions and exacerbations of this puzzling disease.

Cattell⁹⁹⁹ reports an operative mortality of 22 per cent over a twenty year period, and of only 4 per cent during the two years previous to the time of writing. Surgical treatment in properly selected cases is considered a valuable adjunct. The usual indication is failure of the patient to manifest satisfactory improvement on an adequate medical program. Many patients obtain complete relief from the symptoms after simple ileostomy and require no further operation. For those who have incomplete relief or who experience a recurrence later, resection of the colon in stages is indicated¹⁰⁰⁰. MacMahon¹⁰⁰¹ also is impressed with the value of ileostomy. In 4 cases of ulcerative colitis in which ileostomy was required, the skin-grafted iliac stoma, as described by Dragstedt, was established, cutaneous excoriation was

996 Ross, W. D. The Person with Ulcerative Colitis, *Canad. M. A. J.* **58** 326, 1948.

997 Roehlke, A. B., and Tesch, G. Treatment of Ulcerative Colitis with Propylthiouracil, *Minnesota Med.* **31** 418, 1948.

998 Ehrlich, R. Pathogenesis and Treatment of Ulcerative Colitis with Extract of Hog Stomach, *Am. J. Digest. Dis.* **14** 294, 1947.

999 Cattell, R. B. The Surgical Treatment of Ulcerative Colitis, *Gastroenterology* **10** 63, 1948.

1000 Ferguson, L. K., and Welty, R. F. The Surgical Management of Ulcerative Colitis, *S. Clin. North America* **27** 1427, 1947.

1001 MacMahon, C. E. Surgical Aspects of Ulcerative Colitis, *Northwest Med.* **47** 269, 1948.

avoided in each case¹⁰⁰² According to Ault,¹⁰⁰³ approximately 15 to 20 per cent of patients with chronic ulcerative colitis require surgical intervention, these are in advanced stages, resulting from either an acute fulminating illness or a chronic, intermittent process The chief indications are listed as chronic ulcerative colitis with constitutional and visceral degenerative changes, anorectal complications, polypoid degeneration and carcinoma, obstruction and tumor mass, subacute perforation, abscess and fistula Seventy per cent of 20 patients were restored to health by operation

Best¹⁰⁰⁴ expresses a conservative opinion Of the 71 patients seen consecutively over a two year period, only 9 (12 per cent) were subjected to operation, the over-all mortality was 11 per cent The mortality among patients not operated on was 15 per cent Best further states that there is not sufficient evidence at present to conclude that early ileostomy will result in permanent cure of the disease and permit permanent closure of the ileostomy

Dennis and his associates¹⁰⁰⁵ performed vagotomy in 22 cases of idiopathic ulcerative colitis and in 1 case of functional diarrhea One patient died of cardiac complications, without completion of the vagotomy Two patients were worse at the time of the report, 3 were unchanged, 14 were improved and 3 had not been followed long enough for evaluation Two of the excellent results occurred in the cases of patients who also had regional enteritis Of 3 patients whose insulin tests suggested incomplete vagus section, 2 were free of symptoms Patients with long-standing disease and those with considerable fibrosis of the bowel wall seemed to do less well than those in the acute phase and those having good bowel elasticity The authors correctly emphasize that vagotomy should not be employed promiscuously The reviewers, on the basis of present evidence, regard the procedure as empiric and await long term results with interest They have seen 1 patient in whose case a temporary remission occurred after vagotomy but who now has experienced a recurrence of the disease

Tuberculosis—Hyperplastic tuberculosis of the colon is described in a European woman of 26, who, ten years earlier, had had pleurisy

1002 Black, B M, and Thomas, J F Skin-Grafted Ileac Stoma, Proc Staff Meet, Mayo Clin **22** 508, 1947

1003 Ault, G W Surgical Treatment of Chronic Ulcerative Colitis, Am J Surg **75** 325, 1948

1004 Best, R R The Consideration for Surgery in Ulcerative Colitis Am J Digest Dis **14** 388, 1947

1005 Dennis, C, Eddy, E D, and Westover, D Vagotomy in Treatment of Idiopathic Ulcerative Colitis and Regional Enteritis, Minnesota Med **31** 253, 1948

and tuberculous glands¹⁰⁰⁶ In the four years prior to operation, slowly progressing symptoms of intestinal stenosis developed At the time of operation, the roentgenogram of the chest was negative A second case is reported in another European¹⁰⁰⁷

Endometriosis—In the third case of endometrioma of the cecum recorded at the Mayo Clinic, the patient had had considerable premenstrual pain¹⁰⁰⁸ Acute symptoms consisted of dull, generalized pain in the lower part of the abdomen, followed with burning, gnawing pain in the right lower abdominal quadrant, anorexia, nausea, vomiting and diarrhea Operation revealed a definite inflammatory reaction about the appendix, the cecum was bound in the pelvis with what appeared to be recently formed adhesions A hard, olive-sized nodule was palpated in the wall of the cecum near the ileocecal valve Microscopic examination disclosed an endometrioma, which was excised Gorse, Bardin and Gibert¹⁰⁰⁹ describe endometriosis of the sigmoid

Radiation Injury—Among 3,392 cases of carcinoma of the cervix uteri in which the condition was treated according to the Stockholm method of irradiation, rectal injuries occurred in 313 (9.2 per cent), in general, these were mild¹⁰¹⁰ The chief cause was an overdose of the radium radiation Maas¹⁰¹¹ estimates that in 50 to 75 per cent of all cases in which women are treated for pelvic malignancy by irradiation, permanent, though perhaps unrecognized, rectal sequelae develop, including slight to extensive scarring, hemorrhage, fistula or complete occlusion In the cases of 19 patients sustaining radiation injury of the intestine during treatment for pelvic cancer, the outstanding early symptom was diarrhea¹⁰¹² Later manifestations included pain, demonstrable ulceration and stricture formation with partial or complete obstruction The early lesions, usually located on the anterior wall of the rectum and the rectosigmoid, were characterized by an edematous, friable mucosa Ulceration, with a grayish white sloughing, was noted later Perirectal fibrosis and obstruction developed ultimately

1006 Brodin, H A Case of Multiple Hyperplastic Tuberculosis of the Colon, *Acta radiol* **28** 227, 1947

1007 Sterin, L, and Sterin, R Tuberculose du côlon droit a forme sténosante, *Presse méd* **19** 222, 1947

1008 Irons, W E, Judd, E S, Jr, and Dockerty, M D Endometrioma of the Cecum Report of a Case, *Proc Staff Meet, Mayo Clin* **22** 530, 1947

1009 Gorse, J M, Bardin, P, and Gibert, T Endometriose du côlon sigmoïde Resection en un temps, *Arch d mal de l'app digestif* **36** 604, 1947

1010 Ingelman-Sundberg, A Rectal Injuries Following the Stockholm Method of Treatment of Cancer of the Cervix Uteri, *Acta radiol* **28** 760, 1947

1011 Maas, J M Intestinal Changes Secondary to Irradiation of Pelvic Malignancies, *Am J Obst & Gynec* **56** 249, 1948

1012 Hock, C W, Rodrigues, J, Hamann, A, and Palmer, W L Radiation Injuries of the Intestines, *Am J Med* **4** 511, 1948

Perforation—Uriburu¹⁰¹³ discusses perforation in detail. A swallowed toothpick perforated the sigmoid, entered a corpus luteum cyst of the left ovary and resulted in obstructive symptoms, with roentgenologic findings leading to a preoperative diagnosis of carcinoma of the sigmoid¹⁰¹⁴

Sulfonamide and Antibiotic Drugs—End to end anastomosis of the descending colon was performed on 16 control dogs, 16 were given succinylsulfathiazole (sulfasuxidine®) before and after operation, and 12 received both sulfasuxidine® and streptomycin¹⁰¹⁵. An open technic was used on 18 treated and 12 control animals and a closed technic, on 10 treated and 4 control animals. The process of healing was then studied at intervals after operation. Among the control dogs, there was a high percentage of wound infection and peritonitis, with 3 perforations and 3 deaths. All the treated animals survived, there were no wound infections, perforations or instances of peritonitis.

Phthalylsulfathiazole (sulfathalidine®), in doses of 3 to 5 Gm daily, is reported to have benefited the majority of 481 patients undergoing anorectal surgery, the majority of 23 patients with ulcerative colitis and 11 patients with diverticulitis¹⁰¹⁶. On the basis of other studies and personal experience, the reviewers question the omnipotence attributed to sulfathalidine®. Preliminary studies of newer sulfonamide drugs seem to establish succinylsulfathiazole as a potentially useful drug in infections of the bowel¹⁰¹⁷. Penicillin insufflated into the rectum or applied in cocoa butter capsules is apparently absorbed as well as penicillin introduced into the upper part of the bowel¹⁰¹⁸.

Miscellaneous Conditions—Wyman¹⁰¹⁹ reports 2 interesting cases of interposition of the colon between the diaphragm and the liver. A colocolic invagination without evident pathologic basis is reported¹⁰²⁰.

1013 Uriburu, J. V., Jr. Perforacion patologica del colon ilio-pelviano, *Cirugia* **1** 73, 1947.

1014 Meltzer, A., and Hackell, D. B. Foreign Body Perforation of the Sigmoid Simulating Carcinoma, *Am J Surg* **74** 824, 1947.

1015 Poth, E. J., McNeill, J. P., Manhoff, L. J., King, W. B., and Sinclair, J. G. The Healing of the Bowel as Influenced by Sulfasuxidine and Streptomycin, *Surg, Gynec & Obst* **86** 641, 1948.

1016 Angelo, G. Sulfathalidine in Intestinal Disease, *Rev Gastroenterol* **15** 145, 1948.

1017 Florestano, H. J., and Bahler, M. E. Investigations of Some Newer Sulfonamides as Intestinal Chemotherapeutic Agents, *J Pharm & Exper Therap* **92** 196, 1948.

1018 Mandel, E. E., and Thayer, J. D. Rectal Absorption of Penicillin, *J Lab & Clin Med* **33** 135, 1948.

1019 Wyman, A. C. Asymptomatic Hepatodiaphragmatic Interposition of the Colon, *Gastroenterology* **9** 213, 1947.

1020 Joyeux, R., and Courty, A. Les invaginations intestinales colo-coliques essentielles, *Arch d mal de l'app digestif* **36** 580, 1947.

In 1 case, a granulomatous tumor encircled and moderately obstructed the descending colon¹⁰⁻¹ Microscopic examination disclosed pronounced thickening and fibrosis, with no evidence of malignancy Venereal lymphogranuloma produced complete obliteration of the rectum¹⁰²² Ectass and Van Lerberghe¹⁰²¹ describe a case of simple ulcer of the colon

Polyps and Other Tumors—Gardner¹⁰⁻¹ discusses hereditary polyposis of the colon as a mendelian dominant predisposition to excessively rapid growth of the intestinal epithelium, leading to hyperplasia, adenomas and carcinoma Four patients were treated by colectomy and ileo-rectal anastomosis According to Dukes,¹⁰²⁵ the villous papilloma probably arises as a proliferation of superficial glandular epithelium, whereas the adenoma probably originates in deeper situated epithelial cells in the crypts The adenoma is regarded as more liable to neoplasia than the papilloma

The demonstration of a pedicle or of dimpling of the bowel wall is sufficient for the diagnosis of a single polypoid lesion, according to Swenson and Wigh¹⁰²⁶ Much emphasis is placed on the need for careful and repeated study of the colon in cases of obscure bleeding Colvert and Brown¹⁰²⁷ review 235 cases of rectal polyps with a five year follow-up of 174 The lesions rarely produce symptoms indicative of their presence, malignancy, when it exists is usually of a low grade Among 117 cases in which benign polyps were removed, carcinoma of the rectum subsequently developed in 25 per cent Of 43 cases in which polyps were not removed, carcinoma of the rectum developed within five years in 65 per cent It is concluded that rectal polyps are malignant at the onset or tend to become so relatively early Bacon and Broad¹⁰²⁸ reemphasize the close relationship between intestinal adenomas and carcinomas in respect to age incidence, frequent location

1021 Meyer, A C, and Judd, E S, Jr Granulomatous Tumor of the Descending Colon Simulating Carcinoma Report of a Case, Proc Staff Meet, Mayo Clin **23** 291, 1948

1022 Ameline, A, and Savignac, R Un nouveau cas d'obliteration totale d'une stenose du rectum, Arch d mal de l'app digestif **37** 252, 1948

1023 Ectass, L, and Van Lerberghe, R L'ulcere simple du colon, Acta Gastroenterol belg **10** 118, 1947

1024 Gardner, C M Polyposis of the Colon, Arch Surg **56** 75 (Jan) 1948

1025 Dukes, C E An Explanation of the Difference Between a Papilloma and an Adenoma of the Rectum, Proc Roy Soc Med **40** 829, 1947

1026 Swenson, P C, and Wigh, R The Role of the Roentgenologist in the Diagnosis of Polypoid Disease of the Colon, Am J Roentgenol **59** 108, 1948

1027 Colvert, J R, and Brown, C H Rectal Polyps Diagnosis, Five Year Follow-Up, and Relation to Carcinoma of the Rectum, Am J M Sc **215** 24, 1948

1028 Bacon, H E, and Broad, G G Pathogenesis of Adenomatous Polyps in Relation to Malignancy of Large Bowel, Rev Gastroenterol **15** 284, 1948

in rectum and sigmoid, and frequent coexistence in the same person, they should be treated as premalignant lesions Swinton,¹⁰²⁹ Binkley and Sunderland,¹⁰³⁰ and Schlicke¹⁰³¹ express similar views Of 368 polyps of the rectum Bournel and Hermann¹⁰³² found 29 to be neoplastic

Wyatt and Goldenberg¹⁰³³ report the cases of male twins with familial polyposis of the colon, who died at 26 of carcinoma of the rectosigmoid Generalized adenomatosis of the colon was observed in the cases of a mother and daughter¹⁰³⁴ The mother and all 6 adult children of one family had either multiple polyposis of the colon or carcinoma of the sigmoid or rectum, or both¹⁰³⁵ Five instances of polyposis of the colon in two families are described by Guptill¹⁰³⁶ An unusual case of multiple polyposis of the colon, secum, vermiform appendix and rectum is presented¹⁰³⁷ Pathologic study disclosed both malignant and nonmalignant polyps, carcinoma of the cecum and a malignant adenoma of the appendix "Cleansing" the rectum and the rectosigmoid colon of polyps by electrocoagulation, anastomosing the ileum to this segment and removing the remainder of the colon are recommended as effective therapy¹⁰³⁸, the remaining areas of the colon and rectum can thus be observed and recurring polyps treated Three polypoid tumors of the rectosigmoid colon apparently were treated successfully by contact radiotherapy¹⁰³⁹

1029 Swinton, N W The Significance and Frequency of Benign Polyps of the Colon and Rectum, *Am Pract* **2** 603, 1948, Diagnosis and Treatment of Mucosal Polyps of the Rectum and Colon with Early Malignant Change, *Am J Surg* **75** 369, 1948

1030 Binkley, G E, and Sunderland, D A Diagnosis and Treatment of Papillary Adenomas of the Rectum, *Am J Surg* **75** 365, 1948

1031 Schlicke, C P Polyps of the Large Intestine, *Northwest Med* **47** 276, 1948

1032 Bournel, J, and Hermann, G Les tumeurs, vilieuses deu rectum generatives de cancers rectaux, *Acta Gastroenterol belg* **10** 89, 1947

1033 Wyatt, J P, and Goldenberg, H Malignancy Developing in Familial Polyposis of Colon in Male Twins, *Canad M A J* **58** 603, 1948

1034 Bonorino-Udaondo, C, Chimento, A, and Coppola, J A Adenomatosis colonica generalizada familiar, *Arch argent de enferm d ap digest y de la nutricion* **22** 141, 1947

1035 Estes, W L, Jr Familial Polyposis and Carcinoma of the Colon, *Ann Surg* **127** 1035, 1948

1036 Guptill, P Familial Polyposis of the Colon, *Surgery* **22** 286, 1947

1037 Maisel, B, and Foot, N C Multiple Polyposis of the Colon with Malignant Change Involving Colon and Appendix, *Ann Surg* **126** 262, 1947

1038 Charrier, J, Hillemand, P, and Hartmann, L A propos du traitement de la polypose rectocolique essentielle generalisee, *Arch d mal de l'app digestif* **36** 5, 1947

1039 Crismer, R, and Ramonil, L Tumeurs vilieuses recto-sigmoïdiennes et radiotherapie de contact (note preliminaire), *Acta gastroenterol belg* **10** 489, 1947

A cavernous angioma of the cecum simulated a polyp, with intestinal bleeding¹⁰⁴⁰ A submucous lipoma of the transverse colon produced obstruction and intussusception¹⁰⁴¹

Carcinoma—The rather extensive literature dealing with carcinoma of the colon indicates a continued rise in the rate of operability and a decrease in the mortality Although the subject has been widely discussed, there appears to have been little significant progress in the earlier recognition of the disease As in previous years, there remains an insufficient awareness of the frequency of carcinoma of the colon and too infrequent use of the examining finger and the proctoscope In this connection, the reviewers wish to emphasize the value of routine proctosigmoidoscopy in the recognition of asymptomatic malignant adenomas of the rectum and sigmoid The failure to diagnose "early" cancer of the colon is all the more regrettable in view of the comparatively favorable prognosis accompanying successful resection

More than half (54.3 per cent) of all patients with carcinoma of the large intestine seen at the Mayo Clinic had lesions palpable by digital examination¹⁰⁴² About a fourth (23 per cent) had received some form of treatment for disease of the colon or rectum, and not for carcinoma An additional 16.2 per cent had lesions within reach of the sigmoidoscope, a fourth of this group likewise had received treatment for some condition other than the carcinoma Cases of carcinomas beyond the reach of the examining finger and the sigmoidoscope constituted the remaining 29.5 per cent of the total series, the diagnosis in 28.4 per cent was established by roentgenologic examination and in 1.1 per cent, at operation Sixty-nine per cent of cancers of the colon in 441 cases reported by Kleckner¹⁰⁴³ were within reach of the examining finger A change in bowel habit was the earliest symptom in 304 A time lag of more than one year from the time of the initial symptom until medical advice was sought was noted in 142 cases One hundred patients had been treated for diseases, principally of the rectum or colon, other than carcinoma, after the first symptoms of malignancy had appeared In 100 consecutive cases of carcinoma of the rectum and anus, the average duration of illness before the patients

1040 Lazarus, J. A., and Marks, M. S. Benign Tumors of Vascular Origin, *Surgery* **22** 766, 1947

1041 Dallos, A. Submucous Lipoma of Transverse Colon with Intussusception, *Am J Digest Dis* **14** 345, 1947

1042 (a) Jackman, R. J. Diagnostic Errors in Carcinoma of the Large Intestine, *Proc Staff Meet, Mayo Clin* **22** 447, 1947 (b) Jackman, R. J., Neibling, H. A., and Waugh, J. M. Carcinoma of the Large Intestine Diagnostic Errors in Relation to Location of Lesion, *J A M A* **134** 1287 (Aug 16) 1947

1043 Kleckner, M. S. Proctologic Surgery of the Large Bowel, *J A M A* **35** 545 (Nov 1) 1947

were first seen was nine and nine-tenths months, the commonest symptoms were rectal bleeding and change in bowel habit. The mortality rate in 69 cases in which patients were subjected to radical resection was 29 per cent¹⁰⁴⁴

A statistical analysis of 844 cases of carcinoma of the rectum and rectosigmoid revealed bleeding and a loss of more than 10 pounds (4.5 Kg) in weight as the commonest symptoms¹⁰⁴⁵. The average duration of symptoms from the alleged time of onset of illness until the patient sought medical aid was seven months. The resectability rate for the period from 1931 to 1940 was only 20 per cent, for the period from 1940 to 1946, it was 45.6 per cent. The mortality rate in the latter period was 9.6 per cent. Combined abdominoperineal resection was the operation of choice. Adequate irradiation of the lesion is thought to have prolonged life.

Coller and Berry¹⁰⁴⁶ state that more than 97 per cent of patients with carcinoma of the colon have vague symptoms of indigestion, abdominal distress, bleeding from the rectum or a change in bowel habits. Every patient with these symptoms should be given a barium sulfate enema and a sigmoidoscopic examination, as should every patient with hemorrhoids. Further improvement in the prognosis in cancer of the colon lies principally in earlier diagnosis. Complete and thorough periodic physical examination offers the best opportunity to detect carcinoma in its curable stage. Martin¹⁰⁴⁷ and Hendrick and Adams¹⁰⁴⁸ express similar views. The importance of rectal bleeding and the need for prompt sigmoidoscopy are again emphasized by Shedrow¹⁰⁴⁹ and by Swinton and Pyrttek¹⁰⁵⁰.

The roentgenologic diagnosis is reviewed by Hughes and O'Malley,¹⁰⁵¹ with particular emphasis on the mucosal pattern of the

1044 Guzzetta, P. C., Jr., and Cole, W. H. Carcinoma of the Rectum and Anus, *Am Pract* **2** 71, 1947

1045 Thomas, R. H., Kline, P. S., and Seed, L. Carcinoma of the Rectum and Rectosigmoid. A Statistical Analysis of Eight Hundred and Forty-Four Cases, *Arch Surg* **56** 92 (Jan) 1948

1046 Coller, F. A., and Berry, R. L. Cancer of the Colon, *J A M A* **135** 1061 (Dec 20) 1947

1047 Martin, J. L. Problem of Carcinoma of the Colon in the Southeast, *South Surgeon* **14** 7, 1948

1048 Hendrick, J. W., and Adams, T. R. Factors Influencing Operability of Three Hundred and Thirty-Seven Carcinomas of the Colon and Rectum, *Texas State J Med* **43** 641, 1948

1049 Shedrow, A. Rectal Hemorrhage and Early Diagnosis of Cancer, *South African M J* **21** 604, 1947

1050 Swinton, N. W., and Pyrttek, L. J. Rectal Bleeding, *S Clin North America* **28** 793, 1948

1051 Hughes, C. R., and O'Malley, E. J. Roentgenologic Diagnosis of Tumors of the Large Intestine, *M Clin North America* **32** 428, 1948

bowel When the roentgenologic findings are not conclusive or when there is a persistence of symptoms, the examination should be repeated An air contrast-barium sulfate enema study should be employed when polyps are found on proctoscopy Davis and Daniel¹⁰⁵² advocate surgical intervention when persistent bleeding is noted at proctoscopy, even when the roentgenologic findings are negative

Grossly, carcinoma of the right portion of the colon is papillary in character, frequently developing into a large, friable, cauliflower-like lesion, which bleeds easily¹⁰⁵³ Secondary infection and anemia are not uncommon Common symptoms are pain, "dyspepsia," weakness and change in bowel habit An abdominal mass can be palpated in approximately 75 per cent of cases Fifteen per cent of patients found to have carcinoma of the right portion of the colon had undergone appendectomy after the onset of symptoms Pain was the predominant presenting feature in 60 cases¹⁰⁵⁴ Diarrhea was present in only 20 per cent Seventy-nine per cent of patients had anemia but only 54 per cent showed hemoglobin content of less than 11 Gm per hundred cubic centimeters The average duration of symptoms before operation was six and one-half months Thirty-two per cent of patients had an annular type of growth and 25 per cent, an obstructive and constricting lesion The immediate postoperative mortality was 8 per cent Seventy-one per cent of those patients with no obvious metastases were living, at an average, three to eight years after operation and 29 per cent of those with metastases were surviving, at an average, four years after operation The clinical manifestations are also discussed by Sanders¹⁰⁵⁵ and Sprenger¹⁰⁵⁶

A detailed and highly interesting survey was made of 813 cases of tumors of the gastrointestinal tract in army personnel between the ages of 18 and 38¹⁰⁵⁷ There were 441 carcinomas, of which 77 per cent involved the large intestine Approximately half of these were in the rectum Most tumors occurred in the age group from 31 to 38, but there were 26 epithelial cancers in the 18 to 20 age group There were 7 cases of carcinoma of the appendix, a condition usually diagnosed

1052 Davis, K A, and Daniel, W H Problems in the Diagnosis of Cancer of the Colon, *Radiology* **49** 50, 1947

1053 Mayo, C W Carcinoma of the Right (Proximal) Portion of the Colon *S Clin North America* **27** 875, 1947

1054 Brown, C H, Colvert, J R, and Brush, B E Clinical Aspects of Carcinoma of the Cecum and Ascending Colon Report of Sixty Cases, *Ann Int Med* **28** 940, 1948

1055 Sanders, L C The Early Diagnosis of Carcinoma of the Colon and Rectum, *Rev Gastroenterol* **15** 193, 1948

1056 Sprenger, L A Carcinoma of the Large Bowel, *Illinois M J* **93** 92, 1948

1057 Ehrlich, J C, and Hunter, O B, Jr Tumors of the Gastrointestinal Tract, *Surg, Gynec & Obst* **85** 98, 1947

clinically as acute appendicitis. The high incidence of carcinoma of the colon and rectum is actually greater, because the authors did not classify "adenoma malignum" and "adenomatous polyp with early carcinomatous transformation," in which no evidence of invasion could be found, as carcinoma, but as polyps. Cases of adenomatous polyps totaled 138, with suggestive evidence of malignancy in 10. One hundred and five of these tumors were in the rectum. There were 76 carcinoid tumors, 65 involving the appendix, 10, the rectum, and 1, the stomach. The condition in 53 cases was designated as benign lymphoid polyp of the rectum.

An adenocarcinoma of the cecum, free from metastases, was associated with a carcinoid of the ileum, producing lymphatic metastases.¹⁰⁵⁸ A primary adenocarcinoma in the cecum metastasized to the lung, the pulmonary lesion underwent central necrosis and cavitation.¹⁰⁵⁹ A white woman of 70, who ten years previously had undergone colectomy on the right for carcinoma of the cecum, was found to have advanced carcinoma of the sigmoid.¹⁰⁶⁰ A case of ulcerating carcinoma of the sigmoid in an obese, well nourished woman is described.¹⁰⁶¹ The roentgenologic picture was unusual in that it presented little or no changes in contour, with multiple polypoid-like defects involving approximately 6.5 cm of the sigmoid. At operation, the lesion in the sigmoid was found to contain a large longitudinal ulceration, covering the entire intramucosal surface of the tumor. The polypoid-like, smooth intraluminal defects observed roentgenologically were produced by the elevation of the edges of the ulceration. The oval, ulcerating tumor extended longitudinally, in contrast to the usual annular type. Two simultaneously growing primary carcinomas, one an adenocarcinoma of the sigmoid with metastases and the other a papillary cyst adenocarcinoma of the ovary, together with a leiomyoma uteri, were discovered in 1 case.¹⁰⁶²

Forty¹⁰⁶³ reports 2 cases, in each of which carcinomas involved both the colon and the rectum. Four resections for carcinomas of the

1058 Morgan, C. N. Carcinoma of the Cecum Associated with Carcinoid Tumor of the Small Intestine, *Proc Roy Soc Med* **40** 874, 1947.

1059 Johannsen, M. W. Adenocarcinoma of the Cecum with Involvement of the Lungs, *New York State J Med* **47** 2000, 1947.

1060 Reichman, H. R. Multiple Malignant Lesions of the Colon, *Am J Surg* **75** 275, 1948.

1061 Feldman, M., Gann, M. E., and Weinberg, T. Ulcerating Carcinoma of the Sigmoid. Report of a Case with an Unusual Roentgen Picture, *Gastroenterology* **10** 1018, 1948.

1062 Hanson, K. B., and Crane, J. T. Simultaneous Occurrences of Multiple Primary Carcinomas Within the Abdominal Cavity, *Am J Surg* **74** 895, 1947.

1063 Forty, F. Associated Carcinoma of Colon and Rectum, *Proc Roy Soc Med* **40** 872, 1947.

colon arising from three different sites were required in 1 case over a period of nineteen years, the patient outlived two of his surgeons¹⁰⁶⁴ Sheinfeld¹⁰⁶⁵ also describes multiple colonic lesions

A carcinoma of the descending colon was complicated by the formation of a fistula into the ileum, the abdominal wall and the mesocolic lymph nodes were involved¹⁰⁶⁶ An extensive resection of the involved structures led to improvement, but at a later operation, extensive retroperitoneal metastases were noted A case of ileocolic fistula secondary to malignant disease was managed by combined resection of a portion of the ileum and the colon¹⁰⁶⁷ Interesting case studies are reported also by Gutmann and others,¹⁰⁶⁸ Estrada and Nery,¹⁰⁶⁹ and Dascalakis¹⁰⁷⁰

Recent advances in surgical management are discussed by Allen and his associates¹⁰⁷¹ The reduced mortality is attributed to the correction of anemia and hypoproteinemia, the use of vitamins, decompression of the bowel, and to chemotherapy and antibiotic drugs¹⁰⁷²

In a series of 488 cases in which bowel resection was done, 346 operations were performed prior to January 1946, with 15 deaths (6.4 per cent), and 142, subsequent to that date, with no deaths¹⁰⁷³ A combination of phthalylsulfathiazole and streptomycin is regarded as the best preoperative antibacterial agent The resectability rate in 336

1064 Edwards, M Four Metachronous Malignant Lesions of the Colon, *Surgery* **23** 808, 1948

1065 Sheinfeld, W Synchronous Colon Carcinomas of Multicentric Origin, *New York State J Med* **48** 85, 1948

1066 Stralinger, A Ileocolic Fistula Due to a Cancer of the Descending Colon Operative Results, *Am J Digest Dis* **14** 371, 1947

1067 Vinci, V J, McLeod, C E, and LaBella, L O Spontaneous Ileocolic Fistula A Complication of Carcinoma, *Ann Surg* **126** 246, 1947

1068 Gutmann, R A, Beaugard, G, and Parturier-Lannegrace, M Deux cas de cancer du rectum a la periode de debut, *Arch d mal de l'app digestif* **36** 420, 1947

1069 Estrada, J, and Nery, P T Cancer of the Rectum, *J Philippine M A* **23** 283, 1947

1070 Dascalakis, T Amibiase et cancer du rectum, *Arch d mal de l'app digestif* **36** 410, 1947

1071 Allen, A W, Welch, C E, and Donaldson, G A Carcinoma of the Colon, *Ann Surg* **126** 19, 1947

1072 Ravdin, I S, Zintel, H A, and Bender, D H Adjuvants to Surgical Therapy in Large Bowel Malignancy, *Ann Surg* **126** 439, 1947 Edwards, M Present-Day Trends in the Surgical Treatment of Carcinoma of the Large Intestine *South M J* **41** 162, 1948 Pemberton, J deJ The Effect of Chemotherapy on Surgery of Malignant Lesions of the Colon, *Proc Staff Meet, Mayo Clin* **22** 561, 1947

1073 Bacon, H E, and Rowe, R J Surgery of Lower Bowel Preparation and After-Care of Patient, *J A M A* **136** 975 (April 10) 1948

cases of cancer of the rectum and the rectosigmoid was 75 per cent, in 71.7 per cent of those cases in which resection was done, the Miles operation was found to be applicable.¹⁰⁷⁴ In 167 cases, the one stage, combined abdominoperineal resection of the rectum was performed, with 9 postoperative deaths, a mortality of 5.3 per cent, this mortality rate is satisfactory so long as the range of resectability is high, emphasizing again that efforts must be directed more forcefully than ever to earlier diagnosis.

Binkley and Deddish¹⁰⁷⁵ report an operative mortality of 2.3 per cent in 350 consecutive cases of abdominoperineal resection. Genitourinary complications occurred in 46 per cent. Coronary occlusion, pulmonary embolism, peritonitis, phlebothrombosis and thrombophlebitis were the most important complications. Jones and his co-workers¹⁰⁷⁶ report 100 consecutive cases in which abdominoperineal resection was done without a fatality. No sulfonamide or antibiotic drugs were employed in preparation. An uneventful postoperative course was noted in 48 per cent, paralytic ileus or mild obstruction of the small bowel occurred in 9 per cent. Wound complications were not common. The most consistent and troublesome complication was infection of the urinary tract and retention of urine.

Babcock¹⁰⁷⁷ describes a technic in which the portion of the sigmoid above the cancer is brought down to the anus and a functional anus retained. Campbell¹⁰⁷⁸ presents a new method. Gardner¹⁰⁷⁹ emphasizes the advantages of the one stage, "two team" abdominoperineal resection.

Lynch and Hamilton¹⁰⁸⁰ describe an operative technic designed for use in those cases in which the tumor is too low to permit removal by anterior resection and anastomosis. Among the first 50 patients so treated, there were 5 operative deaths.

1074 Rankin, F. W., and Johnston, C. C. Surgical Treatment of Cancer of the Rectum and Rectosigmoid, *J. A. M. A.* **136** 371 (Feb. 7) 1948.

1075 Binkley, G. E., and Deddish, M. R. Complications of Adominoperineal Resection of Rectum for Cancer, *New York State J. Med.* **47** 2547, 1947.

1076 Jones, T. E., Robinson, J. R., and Meads, G. B. One Hundred and Thirty-Seven Consecutive Combined Adominoperineal Resections Without Mortality, *Arch. Surg.* **56** 109 (Jan.) 1948.

1077 Babcock, W. W. Radical Single Stage Extirpation for Cancer of the Large Bowel, with Retained Functional Anus, *Surg., Gynec. & Obst.* **85** 1, 1947.

1078 Campbell, D. D. Carcinoma of the Left Colon, *Canad. M. A. J.* **57** 537, 1947.

1079 Gardner, C. Problems of the Treatment of Carcinoma of the Rectum, *Canad. M. A. J.* **58** 454, 1948.

1080 Lynch, J. M., and Hamilton, G. J. The Lynch Operation for Carcinoma of the Rectosigmoid, *Am. J. Surg.* **74** 3, 1947.

Of 337 patients with carcinoma of the colon and rectum, 307 were followed for at least ten years¹⁰⁸¹ Eighty-one of the 103 patients with carcinoma of the colon underwent some type of resection Of those without obvious metastases, 64.3 per cent survived for five years without recurrence In the group with more extensive lesions, the five year survival rate was 14.8 per cent Two hundred and thirty-four patients had carcinoma of the rectum and the rectosigmoid, of this group 146 underwent some type of resection The five year survival rate was 60 per cent in the group with limited lesions and 30.2 per cent in the group with more extensive carcinomas It is suggested that 50 per cent of patients without involvement of the mesenteric lymph nodes may expect permanent cure In a study of 200 cases in which resection was done for carcinoma of the colon, 57 per cent of patients were alive after five to ten years¹⁰⁸² Seven of 153 tumors below the promontory of the sacrum metastasized in a retrograde manner Fretheim¹⁰⁸³ reviews 114 cases, radical operation was performed in 59 per cent, with a mortality rate of 16 per cent Five year survival rates were 25 per cent in cancer of the right colon and 59 per cent in cancer of the left colon

In 214 cases, the operative mortality was 18.2 per cent¹⁰⁸⁴ Follow-up observations, available in 60 per cent of the cases in which radical resection was done, indicated that 25 per cent of the patients were alive and well five to twenty-five years after operation Of 71 lesions, 49 were considered operable¹⁰⁸⁵ Among the 45 patients who underwent radical resection, there was 1 death Five patients survived five years or more, 13 were alive and well three or more years after operation Judd¹⁰⁸⁶ comments on the improvement in the resectability rate

Hoxworth and Mithoefer¹⁰⁸⁷ advocate resection and immediate anastomosis, the mortality rate in 87 cases in which resection was done was 6.9 per cent Hinton and Localio¹⁰⁸⁸ express the same

1081 Colcock, B. P. Prognosis in Carcinoma of the Colon and Rectum, *Surg., Gynec. & Obst.* **85** 8, 1947

1082 Gilchrist, R. K., and David, V. C. Prognosis in Carcinoma of the Bowel, *Surg., Gynec. & Obst.* **86** 359, 1948

1083 Fretheim, B. Cancer of the Colon, *Acta chir. Scandinav.* **96** 345, 1948

1084 Wilensky, A. O. Carcinoma of the Large Intestine, *Rev. Gastroenterol.* **15** 55, 1948

1085 Jameson, J. W., and Mullins, C. R. Carcinoma of the Colon and Rectum, *New England J. Med.* **237** 699, 1947

1086 Judd, E. S. Resection for Lesions of the Right Portion of the Colon, *Proc. Staff Meet., Mayo Clin.* **23** 225, 1948

1087 Hoxworth, P. I., and Mithoefer, U. Management of Cancer of the Colon, *Surgery* **22** 271, 1947

1088 Hinton, J. W., and Localio, S. A. One-Stage Resection and Anastomosis of the Colon, *Ann. Surg.* **127** 12, 1948

opinion. Of 142 patients, 93 were subjected to some form of radical operation, with a mortality of 12.9 per cent.¹⁰⁸⁹ Of 107 patients, 16 were admitted to the hospital with peritonitis or abscess formation and 29, with symptoms of acute ileus.¹⁰⁹⁰

On the basis of a survey of the work of fifty experienced surgeons, Graham¹⁰⁹¹ notes a trend toward primary anastomosis. Bacon and Smith¹⁰⁹² review anatomic studies of the arterial pattern of the terminal colon. If selection is limited to lesions located at least 6 cm above the anus and whose upper limit is at or below the peritoneal reflection, abdominoperineal resection can be carried out and the anal sphincter preserved without jeopardizing the chance of survival and of reasonable expectation of providing the patient with a functional anal outlet.¹⁰⁹³ In a series of 68 cases, nine deaths are reported, all of them occurring prior to 1941, 7 patients in this group were in the seventh decade, or older. Wangenstein and Toon¹⁰⁹⁴ recommend primary resection and anastomosis for all lesions in the rectosigmoid area 14 to 20 cm from the anus. For lesions 8 cm or less from the anus, abdominoperineal resection should be done. The conservative resection is as good as the radical for lesions between 8 and 14 cm above the anus, provided the tumor is not fixed.

During a twenty-five year period, 276 patients with carcinoma of the rectum were seen in Malmo, Finland, 55 per cent of the lesions were operable.¹⁰⁹⁵ In 66 cases, resection was performed in one stage, with preservation of the anal sphincter. The operative mortality was 30 per cent, the percentage of five year cures, 50 per cent. The importance of preserving the anal sphincter is emphasized. Bergeret and others,¹⁰⁹⁶

1089 Hultborn, K. A. Treatment of Cancer of the Colon, *Acta chir Scandinav* **95** 215, 1947

1090 Brandberg, R., and Ekblom, T. Cancer of the Colon and a Detail of Operative Technique, *Acta chir Scandinav* **95** 461, 1947

1091 Graham, A. S. Current Trends in Surgery of the Distal Colon and Rectum for Cancer, *Ann Surg* **127** 1022, 1948

1092 Bacon, H. E., and Smith, C. H. The Arterial Supply of the Distal Colon Pertinent to Abdominoperineal Proctosigmoidectomy, with Preservation of the Sphincter Mechanism, *Ann Surg* **127** 28, 1948

1093 Nickel, W. F., and Chenoweth, A. I. Resection of the Rectum with Preservation of the Anal Sphincter, *Surgery* **23** 480, 1948. Bacon, H. E., and Rowe, R. J. Primary Resection for Cancer of the Lower Bowel, *New York State J Med* **48** 607, 1948

1094 Wangenstein, O. H., and Toon, R. W. Primary Resection of the Colon and Rectum with Particular Reference to Cancer and Ulcerative Colitis, *Am J Surg* **75** 384, 1948

1095 Koch, F. A Contribution to the Operative Treatment (Resection) of Cancer of the Rectum, *Acta chir Scandinav* **95** 145, 1947

1096 Bergeret, A., Champeau, M., and Seylan, H. Le traitement du cancer du rectum par la résection abdomino-endoanale en un temps. Operation de Babcock, *Schweiz med Wchnschr* **78** 132, 1948

Canónico¹⁰⁹⁷ and Mathewson and Richards¹⁰⁹⁸ state that the one stage abdominoendoanal resection for cancer of the rectum is usually preferred. In 100 cases, anterior segmental resection was performed, with concomitant colostomy and end to end anastomosis between the sigmoid and the rectum, the morbidity was great, the mortality rate, 3 per cent¹⁰⁹⁹. In 100 similar cases, patients were treated in a like manner, except that colostomy was not established, the morbidity was considerably less, the mortality rate was 6 per cent, 4 patients succumbing to pulmonary embolism or to cardiovascular disease.

Best¹¹⁰⁰ states that combined abdominoperineal resection may be replaced in many instances by resection and anastomosis. The combined operation is necessary for tumors located less than 3 inches (7.5 cm) from the sphincter, or when there is widespread involvement of the wall of the sigmoid and of the regional lymph nodes. In another paper, Best¹¹⁰¹ indicates that whereas it is known that three and five year cures average approximately 50 per cent with radical abdominoperineal excision, comparable reports on the results of the operations preserving the sphincter are not yet available. The morbidity rate may be higher, because an incontinent posterior sphincter area or a draining fecal fistula is more troublesome than the average abdominal colostomy. Technically, any operation restoring bowel continuity in the rectal region is more difficult and time consuming.

In 55 cases of acute obstruction of the colon, secondary to neoplasm, the mortality rate was 33 per cent¹¹⁰². Benson¹¹⁰³ discusses the method of dealing with large cancers of the colon invading adjacent structures. Dunphy¹¹⁰⁴ emphasizes the fact that recurrent cancer of the rectum and

1097 Canónico, A. N. *Cáncer rectosigmoideo y de la porción distal del sigmoideo. Resección y enteroanastomosis primaria, presentación de tres casos*, Prensa med argent **34** 2319, 1947.

1098 Mathewson, C., Jr., and Richards, V. *Resection of the Rectum and Rectosigmoid with Primary Extraperitoneal End-to-End Open Anastomosis*, West J Surg **55** 473, 1947.

1099 Mayo, C. W., and Smith, R. S. *Low Anterior Segmental Resection With or Without Colostomy*, Ann Surg **127** 1045, 1948.

1100 Best, R. *Selection of Operative Procedures to Avoid Colostomy in Carcinoma of Rectum and Rectosigmoid*, Surg, Gynec & Obst **86** 98, 1948.

1101 Best, R. R. *Evaluation of Colorectectomy and Immediate Anastomosis of the Rectum*, Arch Surg **56** 681, (May) 1948.

1102 Michel, M. I. *The Diagnosis and Treatment of Acute Malignant Obstruction of the Large Bowel*, New Orleans M & S J **100** 397, 1948.

1103 Benson, R. E. *The Surgical Treatment of Large Colonic Cancers Which Have Secondarily Invaded Surrounding Structures*, Rocky Mountain M J **45** 32, 1948.

1104 Dunphy, J. E. *Recurrent Cancer of the Colon and Rectum*, New England J Med **237** 111, 1947.

colon is not necessarily hopeless, gratifyingly long periods of arrest may follow reoperation. Four illustrative case reports are presented. Two of the patients were alive and apparently well six years nine months and five years six months after the second operation, respectively, the third died after more than five years of comfort, and the fourth patient was bedridden at the time of the report, five years after operation. The surgical management is further reviewed in many additional papers.¹¹⁰⁵

Colostomy—Cecostomy is the safest and most reliable procedure for immediate relief of acute left-sided obstructions of the colon.¹¹⁰⁶ A tube of skin is employed as the terminal segment of a colostomy opening allowing the use of a mechanical plug for control.¹¹⁰⁷ A simple method of ileocolostomy is described by ten Kate.¹¹⁰⁸ Windham and his associates¹¹⁰⁹ recommend transverse colostomy as a preparatory procedure for the management of various lesions of the left colon.

One hundred patients with permanent colostomy openings were visited at home.¹¹¹⁰ Most of them were in good health and active. Dukes points out that the number of evacuations can be controlled by

1105 MacFee, W. F. The Management of Carcinoma in the Several Parts of the Colon, *Ann Surg* **126**:125, 1947. Allen, A. W. Carcinoma of the Large Intestine, *S Clin North America* **27**:1018, 1947. Heyd, C. G. Surgical Procedure for Carcinoma of the Rectosigmoid and Rectum, *New York State J Med* **47**:2543, 1947. Ottenheimer, E. J. Cancer of the Rectum. Analysis of Cases Occurring in Connecticut During 1935-1945, *New England J Med* **237**:1, 1947. Mayo, C. W. The Surgical Treatment of Carcinoma of the Right Part of the Colon, *Minnesota Med* **30**:1197, 1947. Cole, C. C. Analysis of Thirty-Four Cases of Carcinoma of the Rectum and Rectosigmoid Treated by One Stage Combined Abdominoperineal Resection, *Connecticut M J* **11**:808, 1947. Finsterer, H. Ein Beitrag zur Radikaloperation des Kolonkarzinoms, *Krebsarzt* **2**:336, 1947. Turner, J. Carcinoma of the Rectum, *Australian & New Zealand J Surg* **17**:115, 1947. Canónico, A. N. Técnicas fundamentales de colectomías para la resección del cáncer de colon, *Prensa med argent* **34**:1528, 1947. Joyce, T. M. Carcinoma of the Colon, *West J Surg* **56**:110, 1948. Paus, N. Cancer Coli, *Nord med* **37**:166, 1948.

1106 Howell, J. C. Modern Techniques in Colon Surgery, *S Clin North America* **27**:1416, 1947.

1107 Rank, B. K., and Smith, J., Jr. An Improved Permanent Colostomy, *Surg, Gynec & Obst* **85**:75, 1947.

1108 ten Kate, J. A Simple and Aseptic Method of Ileocolostomy, *Surg, Gynec & Obst* **85**:217, 1947.

1109 Windham, S. W., Ellis, J. T., and Latiolais, S. G. Combined Colostomy and Miller-Abbott Tube in the Preparation of the Left Sided Colon Lesions for Surgery, *South Surgeon* **13**:745, 1947.

1110 Dukes, C. E. Management of a Permanent Colostomy. Study of One Hundred Patients at Home, *Lancet* **2**:12, 1947.

diet, fruit and vegetables should be restricted. The most suitable dressing is a pad of absorbent cellulose wadding, 6 inches (15 cm) square, covered with a nonabsorbable material and kept in place with a simple colostomy belt. Holder and Lewison¹¹¹¹ report observations on 67 soldier-patients who underwent colostomy because of war injuries. Troublesome complications resulted when the colostomy opening was placed too near the iliac crest, when the bowel segment was not adequately mobilized, when the opening was placed too near a coexisting cystostomy wound, when the colostomy aperture was too large and when drainage of the retroperitoneal and the pelvic space was inadequate. When the colostomy openings were closed by end to end anastomosis, the patients had less morbidity and a shorter convalescence than if the closure was done by the spur-crushing technic. A follow-up study of 40 patients with colostomy openings indicated satisfactory control in 27 instances, the importance of establishing regular bowel habits by irrigation is stressed.¹¹¹²

On the basis of an experience with the closure of 72 colostomy openings in cases of battle wounds of the colon, Sanders and his associates¹¹¹³ advocate an intraperitoneal type of closure, with anatomic reconstruction of the colon and the abdominal wall, 70 of these colostomy openings were healed by the fourteenth postoperative day, the remaining 2 later closed spontaneously. Thirty-two colostomy openings and 11 fistulas of the rectum and the descending colon were closed at an Army general hospital.¹¹¹⁴ The intraperitoneal approach to closure is preferable when the exact anatomy of the colostomy opening is not known to the surgeon. Spontaneous closure of fistulas of the large bowel is rare, competent surgical intervention usually is necessary to effect a cure. Usher¹¹¹⁵ describes a technic of closure of the colostomy opening used satisfactorily in 33 cases. Three instances of perforation of the colon following enema through a colostomy opening are reported, a technic to obviate the danger is presented, utilizing a soft rubber catheter through a nipple inserted in the colostomy opening.¹¹¹⁶

1111 Holder, H. G., and Lewison, E. F. Management of Colostomies Performed for War Injuries, *Ann Surg* **126** 253, 1947.

1112 McLanahan, S., and Gilmore, W. E. Colostomies. A Follow-Up Study of Functional Results, *South M J* **41** 408, 1948.

1113 Sanders, G. B., Haffner, H., and Lynn, R. B. The Closure of Colostomies, *Ann Surg* **127** 243, 1948.

1114 Hertz, C. S., and Poer, D. H. Closure of Colostomies and Fistulas of the Large Bowel, *Am J Surg* **74** 163, 1947.

1115 Usher, F. C. Colostomy Closure, *Texas State J Med* **43** 570, 1948.

1116 Davis, C., Jr. Enema Tube Perforation of the Colon, *Ann Surg* **126** 377, 1948.

ANUS AND RECTUM

Congenital Anomalies—A one stage abdominoperineal operation is suggested for use in certain cases of imperforate anus in which the colon cannot be safely reached from the perineum¹¹¹⁷ An 18 hour old male infant born with complete absence of the anus, sphincter, anal canal and rectum, was successfully operated on by bringing down the sigmoid colon to serve as the new anal canal and rectum The boy is now 3 and normal in every other respect¹¹¹⁸ In another case, a dermoid cyst, attached to the anterior rectal wall, presented the appearance of a rudimentary hand¹¹¹⁹ Schofield reports an ischioanal dermoid cyst¹¹²⁰

Pruritus Ani—The importance of psychogenic factors in pruritus ani is again emphasized¹¹²¹ The local application of aluminum hydroxide gel is reported to have provided relief in 95 per cent of 98 cases of "moist" pruritus ani¹¹²² Frankfeldt¹¹²³ found tripeleennamine hydrochloride (pyribenzamine hydrochloride®) of value

Fissures and Fistulas—Whitney¹¹²⁴ states that he regards infection of "semivestigial glands" of the anus as the cause of anal cryptitis, fissure in ano, perianal and ischiorectal abscesses, and fistula in ano Aronsson¹¹²⁵ discusses in detail (182 pages) 782 cases of anorectal infection and 356 of anorectal fistulas, in addition to 53 of his own cases of anorectal fistulas The surgical treatment of chronic anal

1117 Rhoads, J F, Pipes, R L, and Randall, J P A Simultaneous Abdominal and Perineal Approach in Operations for Imperforate Anus with Atresia of the Rectum and Rectosigmoid, *Ann Surg* **127** 552, 1948

1118 Liburt, J Successful Operation for Imperforate Anus and Imperforate Rectum, *Am Surg* **74** 228, 1947

1119 Nigam, R A Case of Dermoid Arising from the Rectal Wall, *Brit J Surg* **35** 218, 1947

1120 Schofield, J D Ischio-Anal Dermoid, *Am J Surg* **75** 278, 1948

1121 Schneider, H C Relation of Functional to Organic Diseases of the Anus, Rectum and Sigmoid Colon, *Am J Surg* **75** 296, 1948 Studdiford, M T, and McLean, L D Pruritus Ani and Vulvae, *New Orleans M & S J* **100** 445, 1948 Seletz, R Rationale of Therapy in Pruritus Ani, *A J Surg* **75** 313, 1948

1122 Friedman, M H F, Haskell, B F, and Snape, W J Treatment of Pruritus Ani by Local Application of Aluminum Hydroxide Gel, *Am J Digest Dis* **15** 57, 1948

1123 Frankfeldt, F M Pyribenzamine Its Role in the Treatment of Pruritus Ani, *Am J Surg* **75** 307, 1948

1124 Whitney, E T Infection of the Anal Glands, *Rev Gastroenterol* **15** 451, 1948

1125 Aronsson, H Anorectal Infections and the Sequelae, Especially Fistulae and Incontinence, *Acta chir Scandinav (supp 135)* **96** 1, 1948

fissure is described by Turell¹¹²⁶ A method is described to facilitate primary healing of the wound after the resection of a fistula in ano¹¹²⁷ Early and complete drainage of acute perianal abscess is recommended¹¹²⁸

Hemorrhoids—Carmel¹¹²⁹ describes a method of plastic repair of the anal region after hemorrhoidectomy In 1 case,¹¹³⁰ five days after the second of two injections for uncomplicated internal hemorrhoids, mesenteric thrombosis was demonstrated at operation

Rectal Prolapse—A variety of surgical procedures are recommended¹¹³¹ A case of an unusually large prolapsed section of the rectum, 8 inches (20 cm) long and 18½ inches (46.25 cm) in circumference, is reported^{1131f}

War Wounds—On the basis of an experience with 41 patients sustaining war wounds of the rectum and the anal sphincter, McCune¹¹³² concludes

(1) sphincter muscle exercises are of great value in improving anal sphincter power, (2) the best operative results are usually obtained in those cases in which torn muscle ends can be approximated, (3) the Stone fascial plastic operation has a definite place [in therapy] if the sphincter ends cannot be found, (4) when no repair of sphincter power can be devised an abdominoperineal resection is probably the procedure of choice

Anorectal Surgery—Hydrogen peroxide, dissolved in glycerin, applied to the lower part of the rectum, the anal canal and the perianal

1126 Turell, R The Surgical Treatment of Chronic Anal Fissure, Surg Gynec & Obst **86** 434, 1948

1127 Kenney, J M A Successful Method for Securing Primary Wound Healing After Resection of Fistulae in Ano Preliminary Report, Ann Surg **126** 320, 1947

1128 Granet, E Is Anal Fistula a Necessary Sequel to Perianal Abscess? New York State J Med **48** 63, 1948

1129 Carmel, A G Modern Surgical Treatment of Hemorrhoids and a New Rectoplasty, Am J Surg **75** 320, 1948

1130 Gass, O C Mesenteric Thrombosis Following the Injection Treatment of Hemorrhoids, Am J Surg **75** 279, 1948

1131 (a) Hayden, E P Prolapse of the Rectum, S Clin North America **27** 1062, 1947 (b) Orr, T G A Suspension Operation for Prolapse of the Rectum, Ann Surg **126** 833, 1947 (c) Dunphy, J E A Combined Perineal and Abdominal Operation for the Repair of Rectal Prolapse, Surg Gynec & Obst **86** 493, 1948 (d) Hayes, H T, and Burr, H B Treatment of Complete Prolapse of the Rectum, Am J Surg **75** 358, 1948 (e) Breidenbach, L, and Lord, J W Operative Treatment of Massive Rectal Prolapse, New York State J Med **48** 1275, 1948 (f) Hunt, C J Prolapse of the Rectum Report of Case, Arch Surg **56** 642 (May) 1948

1132 McCune, W S War Wounds of the Rectum and Anal Sphincter, Surgery **23** 653, 1948

areas after anorectal operation, reduced healing time by approximately one half¹¹³³ Sulfasuxidine® seemed useful after anorectal operations¹¹³⁴ Oxidized cellulose (absorbable gauze) is recommended as an adjunct to the control of postoperative rectal hemostasis¹¹³⁵ McGirney¹¹³⁶ reviews the various factors influencing the healing of anorectal wounds

Miscellaneous Conditions—Bargen¹¹³⁷ points out that rectal pain and spasm associated with intestinal disease may intensify the primary condition and retard healing Bland suppositories inserted after bowel movements not only relieve local distress but often alleviate diarrhea, especially in chronic ulcerative colitis A suppository containing ethyl aminobenzoate U S P (benzocaine®), oxyquinoline sulfate, Peruvian balsam, ephedrine hydrochloride U S P and cocoa butter is recommended Schapiro and Astrachan¹¹³⁸ discuss twenty-six different systemic diseases accompanied with proctologic manifestations, these include Addison's disease, agranulocytosis, diabetes, leukemia, pellagra, periarteritis nodosa, scurvy, syphilis, sprue, subacute bacterial endocarditis and uremia Berkowitz¹¹³⁹ states that the presence of granuloma inguinale should be suspected in every instance of ulceration or granuloma of the anogenital region in which the lesion is resistant to antibiotic drugs and to chemotherapy, a therapeutic trial with stibophen (fuadin®) is recommended MacLeod¹¹⁴⁰ describes the removal, intact, of a 40 watt household electric light bulb from a patient's rectum

Extrinsic Lesions—Marshak,¹¹⁴¹ in a well illustrated article, lists the conditions producing extrinsic pressure defects in the rectosigmoid

1133 Jenkins, J T Effect of Glycerite of Hydrogen Peroxide upon Healing Time in Anorectal Surgery, *Am J Surg* **74** 428, 1947

1134 Skir, I Sulfasuxidine in the Postoperative Care of Anorectal Conditions, *New York State J Med* **48**:1274, 1948

1135 Pruitt, M C Primary Postoperative Hemostatic Prophylactic Dressing in Anorectal Surgery, *Am J Surg* **75** 292, 1948

1136 McGirney, J Factors Influencing the Healing of Anorectal Surgical Wounds, *South M J* **41**:401, 1948

1137 Bargen, J A Rectalgia Associated with Intestinal Disease, *Minnesota Med* **31** 361, 1948

1138 Schapiro, S, and Astrachan, J E Proctological Manifestations in Systemic Disease, *Rev Gastroenterol* **14** 786, 1947

1139 Berkowitz, J Granuloma Inguinale with Perianal Involvement, *New England J Med* **237** 665, 1947

1140 MacLeod, F H Removal of Foreign Bodies in Rectum, *Canad M A J* **57**:488, 1947

1141 Marshak, R J Extrinsic Lesions Affecting the Rectosigmoid, *Am J Roentgenol* **58** 439, 1947

as endometriosis, carcinoma of the cervix, chronic inflammatory disease, ovarian carcinoma and ovarian cysts, effects of radiation therapy, fibroid uterus, sigmoiditis, lymphosarcoma and metastatic carcinoma, retroperitoneal tumors and postoperative adhesions. In a survey of 204 cases of extrarectal or extrasigmoidal mass, Brust¹¹⁴² lists the following distribution of confirmed diagnoses: perirectal or pelvic abscess, 47 cases, pelvic disease (in females), 77, diverticulitis, 74, rectal implants (carcinoma) 23, genitourinary lesions (in males), 20, retroperitoneal sarcoma or carcinomatosis, 11, perirectal tumors, 8, carcinoma of the sigmoid, 20, and presacral cysts and dermoids, 4.

Tumors—Cases of mucinous carcinoma in 3 patients with chronic fistulas are described¹¹⁴³. Among 87 cases of submucosal nodules of the rectum 4 lesions proved to be carcinoid and 2, lymphosarcoma, the remainder were benign lesions, non-neoplastic in nature, the result of injection treatments or inflammatory lesions¹¹⁴⁴. Forty-nine instances of benign lymphoma of the rectum are reported¹¹⁴⁵. The growth is always benign, resembling the adenomatous polyp. A leiomyoma of the rectum arose from the internal anal sphincter¹¹⁴⁶. In 78 cases of epidermoid carcinoma of the anus and rectum, surgical measures or irradiation was used¹¹⁴⁷. Rates for five year cures were 25 per cent with surgical treatment and 5 per cent with radiation. Santy and Dargent¹¹⁴⁸ discuss 29 cases of cancer of the anal canal. Moulouguet¹¹⁴⁹ describes an epithelioma of the rectum. Two cases of malignant melanoma of the anorectal region¹¹⁵⁰ and 1 case of a similar lesion in the rectum¹¹⁵¹ are reported.

1142 Brust, J. C. M. Extrarectal and Extrasigmoidal Masses. *Am J Surg* **75** 380, 1948.

1143 Skir, I. Mucinous Carcinoma Associated with Fistulas of Long-Standing. *Am J Surg* **75** 285, 1948.

1144 Jackman, R. J. Submucosal Nodules of the Rectum. Diagnostic Significance, *Proc Staff Meet, Mayo Clin* **22** 502, 1947.

1145 Li, I. Y. Benign Lymphoma of the Rectum, *Surgery* **23** 814, 1948.

1146 Charles, J. D., and McCarty, R. Leiomyoma Within the Substance of the Sphincter. *Am J Surg* **75** 290, 1948.

1147 Sweet, R. H. Results of Treatment of Epidermoid Carcinoma of the Anus and Rectum, *Surg, Gynec & Obst* **85** 967, 1947.

1148 Santy, P., and Dargent, M. Le cancer du canal anal, *Lyon med* **177** 17, 1947.

1149 Moulouguet, M. P. Epitheliome pavimenteux du rectum. *Arch d mal de l'app digestif* **36** 385, 1947.

1150 Muller, O. Anorectal Malignant Melanomas, *Acta chir Scandinav* **96** 39, 1947.

1151 Moskowitz, L. Malignant Melanoma (Melanosarcoma), *Am J Surg* **75** 283, 1948.

MISCELLANEOUS GASTROINTESTINAL SUBJECTS

Olfactory Acuity and Appetite—Experiments are described by Goetzl and Stone,¹¹⁵² demonstrating the existence in human subjects of diurnal variations in olfactory acuity. Freely selected meals were preceded with a period of increasing acuity of olfaction and followed with one of decreasing acuity. The pattern of these variations was found to be intimately connected with the intake of food. The decrease in olfactory acuity occurred only after ingestion of a meal, the increase failed to occur when food was ingested between meals. In another article, the same authors¹¹⁵³ state that amphetamine sulfate simultaneously produces a decrease in olfactory acuity, a decrease in the sensation of appetite, a decrease in intake of calories and a sensation of satiety. The effectiveness of the drug in subduing the sensation of appetite may be determined by measuring its influence on olfactory acuity. Evidence is presented that non-nutritive materials dispel the desire to eat only transiently by filling the stomach but more thoroughly by filling the intestines¹¹⁵⁴, relatively pure cellulose bulk formers serve this purpose best.

Anorexia Nervosa—Berkman, Weir and Kepler¹¹⁵⁵ in a study of 31 cases, noted that no pitting edema was observed at any time in 15, whereas in 12, edema was present on admission of the patient to the hospital. In severe cases, the serum protein values were within the normal range more often than not. Values lower than normal were encountered in about one third. The serum protein values usually could not be correlated with the presence or absence of edema.

Total Intravenous Alimentation—During total intravenous alimentation, there are small quantities of calcium, phosphorus, nitrogen and potassium in the colon¹¹⁵⁶. Frequent enemas or nausea and vomiting increased the amount of material reaching the colon.

Foods and Dyspepsia—Five hundred apparently normal persons and 122 persons with gastrointestinal disorders were questioned concerning the capacity of sixty-eight different foods to induce digestive

1152 Goetzl, F. R., and Stone, F. Diurnal Variations in Acuity of Olfaction and Food Intake, *Gastroenterology* **9** 444, 1947

1153 Goetzl, F. R., and Stone, F. The Influence of Amphetamine Sulfate upon Olfactory Acuity and Appetite, *Gastroenterology* **10** 708, 1948

1154 Hoelzel, F. Use of Non-Nutritive Materials to Satisfy Hunger, *Am. J. Digest Dis.* **14** 401, 1947

1155 Berkman, J. M., Weir, J. F., and Kepler, E. J. Clinical Observations on Starvation Edema, Serum Protein and the Effect of Forced Feeding in Anorexia Nervosa, *Gastroenterology* **9** 357, 1947

1156 Duncan, L. E., Jr., Mirick, G. S., and Howard, J. E. Total Intravenous Alimentation, *Bull. Johns Hopkins Hosp.* **82** 515, 1948

distress¹¹⁵⁷ In both groups, onions, cabbage, rye bread, fat roast beef, bacon, lard and smoked eel were the commonest offenders Other "irritants" listed were cucumbers, salt herring, dumplings and split peas

Psychosomatic Factors in Gastrointestinal Disease—McKell and Sullivan¹¹⁵⁸ encountered the syndrome of hyperventilation in 29 cases Anxiety appeared to be the most important cause, but abdominal symptoms frequently were the mechanism by which attacks were initiated Whatever the physiologic mechanism, the patient may have bizarre complaints One of the commonest symptoms was "giddiness" Dizziness was present in 27 of the 29 cases, sensation of air hunger, in 22, and palpitation of the heart, in 18 Conn¹¹⁵⁹ describes representative cases of mucous colitis, cardiospasm, peptic ulcer and ulcerative colitis and discusses the psychodynamics involved in each

Sullivan and McKell¹¹⁶⁰ analyze the personality disorders in 500 consecutive cases in ambulatory patients with digestive complaints There were 62 patients with peptic ulcer, 35 with cholelithiasis, 8 with symptom-producing diaphragmatic hernia, 11 with carcinoma and 7 with cirrhosis of the liver The patients were classified in three groups Patients in group 1, which included 42.2 per cent of the total, had nervous indigestion, cyclic vomiting, nervous diarrhea or spastic colon the symptoms were vague, emotional disturbances always preceded or were related to the disorder Those in group 2, which included 29.0 per cent, had peptic ulcer, ulcerative colitis or cardiospasm, symptoms were often localized to an organ or system, the emotional disturbances often preceded, or were related to, the illness Those in group 3, which included 28.8 per cent, had carcinoma, cirrhosis, cholelithiasis or amebiasis, the symptoms usually were localized, emotional disturbances sometimes followed or were unrelated It is pointed out that even the psychosomatic approach may not be all inclusive, the environmental stresses and strains should be assayed

Nonulcer dyspepsia in the Fifth Army's forward area in Italy was intensively studied by a team composed of two gastroenterologists, a radiologist, a psychologist, a nurse trained in psychiatry and a psy-

1157 Hove, H An Examination of Different Kinds of Foods with Regard to Their Power of Producing Dyspeptic Symptoms, *Acta med Scandinav* (supp 206) **130** 481, 1948

1158 McKell, T E, and Sullivan, A J The Hyperventilation Syndrome in Gastroenterology, *Gastroenterology* **9** 6, 1947

1159 Conn, J H Psychogenic Factors in Diseases of Digestion, *Gastroenterology* **9** 399, 1947

1160 Sullivan, A J, and McKell, T E Personality Disorders in Gastroenterology, *Gastroenterology* **9** 524, 1947

chiatrist¹¹⁶¹ Of the 110 patients, 53 were classified as passive, 55 as aggressive and 2 as normal, or average, personality types A "psycho-neurotic reaction" was noted in 93 The three major behavior reactions consisted of (a) functional symptoms due to psychogenic factors in a non-neurotic person, (b) functional symptoms as somatic displacement of insecurity and tension feelings in a neurotic person, and (c) functional symptoms as a concomitant of an anxiety state in a neurotic person Gastrosopic findings of "chronic superficial gastritis" were considered to be of minor importance Without minimizing the importance of these observations, the reviewers merely wish to add the comment that the finding of a contented, well adjusted group of soldiers would have been unusual

A personality study was made of 100 mostly middle-aged, ambulant patients, with gastrointestinal symptoms¹¹⁶² As a group, the patients came from large families and had left school early A conspicuous number were considered to have lacked love and attention during childhood The patients without specific gastrointestinal pathologic conditions had experienced the greatest degree of stress The patients without lesions had similar, but more numerous, symptoms than those with specific lesions Half the patients complained that their marriages were failures and disappointments More maladjusted and immature people were observed in the group without organic disease The variations in character structure were similar to those encountered in a psychiatric clinic or in psychoanalytic practice

Wilen and Poole¹¹⁶³ present data and impressions gathered in the Mediterranean theater The major problems of management and disposition were the chronic enteritides and the chronic nonulcer "dyspepsias" Peptic ulcer was proved in 15 per cent of the cases of chronic "dyspepsia" A well defined anxiety state was present in 30 per cent of the cases of chronic diarrhea of unknown etiology

Kraemer¹¹⁶⁴ comments on the high incidence of dyspepsia in soldiers admitted to the neuropsychiatric service Alvarez¹¹⁶⁵ stresses the importance of diagnosis and treatment of functional disturbances and the necessity of a careful evaluation in order to demonstrate a "nervous

1161 Rosen, S R, Weinberg, H, Keeosian, H, Schwartz, I R, and Halsted, J A Personality Types in Soldiers with Chronic Nonulcer Dyspepsia, *Psychosom Med* **10** 156, 1948

1162 Klein, H R A Personality Study of One Hundred Unselected Patients Attending a Gastrointestinal Clinic, *Am J Psychol* **104** 433, 1948

1163 Wilen, C J W, and Poole, P P Digestive Diseases Observed in General Hospital in the Mediterranean Theatre, *Gastroenterology* **9** 253, 1947

1164 Kraemer, M Dyspepsia in the Army—Mental Disease in Soldiers with Gastrointestinal Complaints, *Mil Surgeon* **102** 292, 1948

1165 Alvarez, W C Common Causes of Indigestion and Abdominal Pain in Patients with Negative Findings, *Canad M A J* **57** 425, 1947

breakdown," constitutional inadequacy, poor eating habits, allergy, "mild insanity," cerebral thrombosis, excessive smoking or a neurosis Of 25 patients with hematemesis and melena,¹¹⁶⁶ 10 had recently been under emotional stress

Swenson and Manges¹¹⁶⁷ discuss the roentgenologic findings in functional disturbances, gradations from pronounced atonicity and dilatation to severe diffuse spasm may be present in the colon in the absence of organic disease

Diagnosis of Gastrointestinal Disease—The significance of loss of weight¹¹⁶⁸ and of the presence of occult blood in the feces¹¹⁶⁹ as indicators of disease is again emphasized Jones¹¹⁷⁰ properly points out that in the differential diagnosis of abdominal pain, an accurate, detailed history of the distress is the most important starting point this must be followed with a careful physical examination, intelligent choice of laboratory aids and careful clinical observation Various writers¹¹⁷¹ stress the importance of the roentgenologic examination

Incidence of Gastrointestinal Disease—A survey of patients admitted to the gastroenterologic service of two Army general hospitals indicated that all types of gastrointestinal disease occur with practically identical frequency in white and Negro soldiers¹¹⁷²

Anemia in Gastrointestinal Disease—Haden and Bortz¹¹⁷³ point out that anemia is a common accompaniment of diseases of the intestinal tract The anemia of sprue and of impaired absorption from the small intestine, due to chronic obstruction, often is macrocytic and responds to liver therapy The anemia due to loss of blood is hypochromic and microcytic, it should respond to the administration of adequate amounts of iron Anemia due to depression of the bone marrow function by

1166 Kirketerp, P Causative Factors in Hematemesis and Melena, *Nord med* **37** 156, 1948

1167 Swenson, P C, and Manges, W E Roentgen Findings in Functional Disturbances of the Gastrointestinal Tract, *Radiology* **50** 365, 1948

1168 Baumeister, C F, and Darling, D D The Significance of Weight Loss as Observed in a Gastrointestinal Clinic, *Gastroenterology* **10** 792, 1948

1169 Paul, W D, and Hamilton, H E The Importance of Occult Blood in the Stool, *Am J Digest Dis* **15** 23, 1948

1170 Jones, T E Differential Diagnosis of Intra-Abdominal Pain, *M Clin North America* **32** 389, 1948

1171 Swenson, P C Mass Survey of the Gastrointestinal Tract, *South M J* **41** 108, 1948 Sosman, M C Roentgen Examination of the Gastrointestinal Tract, *Northwest Med* **47** 263, 1948 Hall, A P The Survey Method of Diagnosing Gastrointestinal Problem Cases, *Ohio State M J* **43** 165, 1947

1172 Kirchner, A A A Gastroenterological Comparison of White and Colored Soldiers, *Rev Gastroenterol* **15** 218, 1948

1173 Haden, R L, and Bortz, D W Anemia in Diseases of the Intestinal Tract, *M Clin North America* **32** 382, 1948

to anemia, infection or other factors is usually normocytic and responds to removal of the cause and to transfusion. In colitis of the nonspecific type, the anemia is due to loss of blood, depression of marrow function and deficient absorption of materials needed for the formation of erythrocytes. The relation of hematologic disturbances to alimentary deficiencies is discussed by Mouriquand and his co-workers¹¹⁷⁴

Congenital Anomalies—The more important advances in the treatment of certain congenital anomalies are reviewed by Olim¹¹⁷⁵. Six cases of duplication of the alimentary tract are described by Donovan and Santulli¹¹⁷⁶, severe hemorrhage was an outstanding manifestation in 4. Gastric dilatation, megacolon and idiocy are reported in identical twin girls¹¹⁷⁷. Two instances of complete transposition of the viscera were discovered during the examination of 175 men¹¹⁷⁸.

Conditions of Mouth—Cheney,¹¹⁷⁹ in a useful article, discusses diagnosis and treatment of common forms of stomatitis. In 7 cases of glosso-dynia, burning of the tongue and dryness of the mouth were attributed to the presence of a thick, ropy, tenacious salivary secretion¹¹⁸⁰. The underlying cause was not evident. Neostigmine bromide U S P, in a dosage of 7.5 mg three times daily, was considered effective in treatment. Forty-seven patients were subjected to gingival biopsy¹¹⁸¹. In 18 cases, the clinical diagnosis of amyloidosis had been made with reasonable certainty, amyloid was present in 14 of these. Amyloid deposits were present in some cases in which results of repeated congo red tests were negative.

Abdominal Pain—Ray and Neill¹¹⁸² studied visceral sensation before and after sympathectomy. The splanchnic nerves and the ganglio-

1174 Mouriquand, G., Edel, V., Chmelo, K., and Zathurecky, J. Les dystrophies inapparentes. Carences alimentaires et troubles de l'hématopoïèse (clinique—expérimentation), *Presse méd* **56** 73, 1948

1175 Olim, C. B. Advances in the Surgical Treatment of Congenital Anomalies in Infants and Children, *South Surgeon* **13** 681, 1947

1176 Donovan, E. J., and Santulli, T. V. Duplications of the Alimentary Tract, *Ann Surg* **126** 289, 1947

1177 Fairweather, D. S., and O'Sullivan, H. J. L. Gastric Dilatation, Megacolon, and Idiocy in Identical Twins, *Arch Dis Childhood* **22**:236, 1947

1178 Derow, J. R., and Stearns, A. L. Report on Two Cases of Complete Transposition of the Viscera, *Mil Surgeon* **101** 139, 1947

1179 Cheney, G. The Diagnosis and Treatment of the Common Forms of Stomatitis, *M Clin North America* **32** 355, 1948

1180 Waldman, S., and Pelner, L. Burning Sensation of the Tongue (Glossodynia). An Analysis of Cases That Are Not Due to Vitamin B Deficiency, *Gastroenterology* **10** 965, 1948

1181 Selikoff, I. J., and Robitzek, E. H. Gingival Biopsy for the Diagnosis of Generalized Amyloidosis, *Am J Path* **23**:1099, 1947

1182 Ray, B. S., and Neill, C. L. Abdominal Visceral Sensation in Man, *Ann Surg* **126** 709, 1947

nated chain were removed from the seventh thoracic nerve through the third lumbar ganglions on one or both sides. The sensation of pain in the stomach and intestines, except in the rectum, extrahepatic biliary tract, pancreas, kidneys and ureters, is mediated wholly by visceral afferent nerves accompanying sympathetic nerves. The kidneys, the ureters and the two sides of the colon have a homolateral sensory supply. The remaining abdominal organs, with the possible exception of the gastric mesentery, have a bilateral sensory supply. Pressure in the small intestine, equivalent to 2 cm of mercury, caused a deep, aching pain. When the balloon was in the jejunum or the upper portion of the ileum, the pain was located at or above the umbilicus, when in the terminal ileum, the pain was sometimes below the umbilicus and occasionally about McBurney's point. Pain reception appears to exist not in the walls of the stomach and intestine, but in the mesenteric-visceral juncture. The loss of the sense of pain in the viscera alters a patient's response to visceral disease. Two patients who had undergone bilateral thoracolumbar sympathectomy sustained perforated peptic ulcers without experiencing pain. Vomiting and signs of acute peritonitis led to the diagnosis and to successful operation.

In observations limited to a few patients over a short period of time, Grimson and his associates¹¹⁸³ suggest that excision of the right celiac ganglion and of part or all of the left celiac and the mesenteric ganglions will significantly interrupt pathways for pain sensibility from the abdomen and can be used as an adjunct to exploratory laparotomy for relief from chronic pain arising in the abdominal viscera. Many patients with paraplegia, with a physiologically complete transection of the spinal cord, cannot perceive any sensory stimulation of the somatic type below the level of the transection but can perceive painful stimulation of the viscera whose sensory fibers are believed to enter posterior roots below the level of transection or compression of the cord¹¹⁸⁴. Herpes zoster may offer a difficult challenge in differentiating causes of abdominal pain¹¹⁸⁵.

Abdominal Epilepsy—According to Moore,¹¹⁸⁶ abdominal epilepsy should be considered in the differential diagnosis of severe recurrent

1183 Grimson, K S, Hesser, J H, and Kitchin, W W. Early Clinical Results of Transabdominal Celiac and Superior Mesenteric Ganglionectomy, Vagotomy, or Transthoracic Splanchnicectomy in Patients with Chronic Abdominal Visceral Pain, *Surgery* **22** 230, 1947.

1184 Hoen, T J, and Cooper, I S. Acute Abdominal Emergencies in Paraplegics, *Am J Surg* **75** 19, 1948.

1185 Bosher, L H, Jr, and Williams, C, Jr. Herpes Zoster and the Surgical Abdomen, *Surgery* **23** 773, 1948.

1186 Moore, M T. Abdominal Epilepsy, *Rev Gastroenterol* **15** 381, 1948.

abdominal pain when the result of thorough search for the usual causes is negative. The diagnosis is based on the history, associated epileptic phenomena, roentgenograms of the skull, electroencephalographic studies and the effects of anticonvulsant drugs.

War Wounds and Abdominal Surgery—Rob¹¹⁸⁷ emphasizes the importance of accurate diagnosis of the abdominal gunshot wound. There were 39 deaths in 113 cases in which laparotomy was performed, and only 1 death in 53 cases in which the abdomen was not opened. The absence of peristaltic sounds, confirmed and reconfirmed, is a positive indication for laparotomy, the presence of peristaltic sounds is a valuable guide to, but not a positive indication for, conservative treatment. Rob¹¹⁸⁸ further confirms the value of abdominal auscultation as a diagnostic aid. According to Welch,¹¹⁸⁹ triage contributed more to the saving of the lives of patients with abdominal wounds than any other single factor. Grace¹¹⁹⁰ describes the successful treatment of 5 patients.

Allen¹¹⁹¹ reviews the recent literature pertaining to all phases of abdominal surgery. Preoperative and postoperative care are outlined by Meiselas¹¹⁹² and Donald.¹¹⁹³ Gelatin sponge and oxidized cellulose were found to have a deleterious effect in open surgery of the colon of dogs; the ill effects were directly proportional to the degree of bacterial contamination.¹¹⁹⁴

Hernia—An umbilical hernia containing the stomach, the colon and the gastocolic mesentery was successfully treated surgically.¹¹⁹⁵ Two cases of hernia are presented,¹¹⁹⁶ with classic histories and findings of

1187 Rob, C. G. The Diagnosis of Abdominal Trauma in Warfare, *Surg, Gynec & Obst* **85** 147, 1947.

1188 Rob, C. G. Auscultation in Acute Abdominal Disease, *Lancet* **2** 720, 1947.

1189 Welch, C. E. War Wounds of the Abdomen, *New England J Med* **237** 156, 1947.

1190 Grace, K. D. Gunshot Wounds of the Abdomen, *South Surgeon* **14** 202, 1948.

1191 Allen, A. W. Abdominal Surgery, *New England J Med* **238** 324 and 364, 1948.

1192 Meiselas, D. A. The Pre- and Postoperative Management of Gastrointestinal Diseases, *Rev Gastroenterol* **14** 717, 1947.

1193 Donald, J. M. Preoperative and Postoperative Supportive Therapy in Gastrointestinal Surgery, *Texas State J Med* **43** 562, 1948.

1194 Laufman, H., and Method, H. Effects of Absorbable Foreign Substance on Bowel Anastomosis, *Surg, Gynec & Obst* **86** 669, 1948.

1195 Orr, T. G. Incarceration of the Stomach in an Umbilical Hernia, *Am J Surg* **74** 96, 1947.

1196 Desmond, A. M., and Hutter, F. Strangulated Obturator Hernia, *Brit J Surg* **35** 1948.

strangulated obturator hernia, both patients were operated on successfully¹¹⁹⁶ An instance of femoral hernia containing part of the stomach in the hernial sac, the fourth known case, is reported by Cave¹¹⁹⁷ Interesting cases are described by Hug¹¹⁹⁸ and Allen¹¹⁹⁹

Pilonidal Cysts—Smith¹²⁰⁰ describes 4 cases of perineal pilonidal cysts

Conditions Involving the Peritoneum—Three patients with symptoms suggesting an acute surgical condition of the abdomen showed laboratory evidence and clinical signs of scurvy¹²⁰¹ In 2, operation disclosed hemorrhage as the cause of the peritoneal irritation The third patient, not subjected to operation, had tetany as well as scurvy The tetanic spasms of the abdominal muscles probably accounted, in part, for the picture of an acute surgical condition, although hemorrhage from scurvy also may have been present All 3 patients gave a history of a diet deficient in ascorbic acid, 2 had alcoholism A case of gas cysts of the peritoneum in a male patient is described¹²⁰² The diagnosis was made at laparotomy for intestinal obstruction, and the involved tissue was removed Symptoms of chronic bowel obstruction appeared two and one-half years later, and, after some delay, operation again revealed gas cysts of the peritoneum, involving two separate sections of bowel The patient died on the eleventh postoperative day The largest cyst measured 6 cm in diameter In another case,¹²⁰³ multiple peritoneal cysts clinically and roentgenographically simulated carcinoma of the cecum

Cramer¹²⁰⁴ made an extensive study of 6 cases of talc granuloma of the peritoneum A fibrous mass with a calcific core was found in a

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- 1197 Cave, P Stomach in a Femoral Hernia, *Brit J Radiol* **21** 143, 1948
- 1198 Hug, E Zwei Falle von Hernia obturatoria incarcerata, *Schweiz med Wehnschr* **77** 741, 1947
- 1199 Allen, J C B Hernia in the Right Iliac Fossa, *M J Australia* **34** 532, 1947
- 1200 Smith, T E Anterior or Perineal Pilonidal Cysts, *J A M A* **136** 973 (April 10) 1948
- 1201 Hines, L E Subperitoneal Hemorrhage from Vitamin C Deficiency Simulating Acute Surgical Abdominal Conditions, *Surg, Gynec & Obst* **85** 214, 1947
- 1202 Parsons, R M, and Parsons, W B Cystic Intestinal Pneumatosis, *Canad M A J* **58** 71, 1948
- 1203 Lord, J W Multiple Peritoneal Cysts Simulating Carcinoma of the Cecum, *New York State J Med* **47** 1607, 1947
- 1204 Cramer, R Talkgranulomatose des Peritoneums, *Gastroenterologia* **73** 129, 1948

patient's peritoneal cavity¹²⁰⁵ Bird and his co-workers¹⁻⁰⁶ state that multiple small, radiolucent shadows in the retroperitoneal space indicate an abscess or a phlegmon

A previously healthy woman of 35 suddenly was seized with severe, diffuse abdominal pain, accompanied with diarrhea and vomiting¹²⁰⁷ The temperature ranged from 38.5 to 39.5 C (101.3 to 103.1 F) and the pulse rate, from 120 to 140 There was free fluid in the abdomen, examination of the fluid revealed 15 neutrophils per hundred cells, 20 eosinophils, 40 mononuclear cells, 1 endothelial cell and 14 eosinophilic endothelial cells The bone marrow contained an increased number of eosinophils Complete clinical recovery occurred spontaneously five days later, the blood and bone marrow pictures were normal, the condition was designated as transient eosinophilic peritonitis Intraperitoneal hemorrhage resulted in 1 case from rupture of an aneurysm of an omental artery and in a second, from rupture of a dilated vein on a uterine fibroid¹²⁰⁸ Keasbey¹²⁰⁹ briefly reviews the literature on primary tumors of the peritoneum and presents reports of 8 representative cases

Conditions Involving the Mesentery—Rives, Strug and Essrig,¹⁻¹⁰ in an excellent paper, discuss mesenteric vascular occlusion and present 6 cases The mortality is extremely high because many patients are at the point of death from cardiovascular disease and because the diagnosis and treatment usually are delayed Pathologically, mesenteric vascular occlusion may be classified as embolic and thrombotic, and as arterial, venous or combined Features that aid in diagnosis are a history of a known predisposing factor, character of onset, early disappearance of peristalsis in suspected intestinal obstruction, pronounced leukocytosis without evidence of peritonitis, and development of shock when all other evidence points to partial obstruction Radical resection of the bowel is essential when gangrene has developed and is advisable in all cases Anticoagulant therapy may prevent mesenteric

1205 Ross, J. A., and McQueen, A. Peritoneal Loose Bodies, *Brit J Surg* **35** 313, 1948

1206 Bird, G. C., Jr., Fissel, G. E., and Young, B. R. A Pathognomonic Roentgen Sign of Retroperitoneal Abscess, *Am J Roentgenol* **59** 351, 1948

1207 Laederich, L., and Mamou, H. Peritonite ascitique fugace à eosinophiles, *Presse méd* **55** 789, 1947

1208 Woodruff, M. F. A. Intraperitoneal Hemorrhage of Unusual Etiology with a Report of Two Cases, *Brit J Surg* **35** 311, 1948

1209 Keasbey, L. E. Primary Tumors of the Peritoneum, *Am J Path* **23** 871, 1947

1210 Rives, J. D., Strug, L. H., and Essrig, I. M. Mesenteric Vascular Occlusion, *Ann Surg* **127** 887, 1948

vascular occlusion and may be of value in postoperative care, but the authors do not recommend it "at this time" as definitive treatment

Four cases of thrombosis of the superior mesenteric vessels are reported in which plain roentgenograms of the abdomen demonstrated distention of the right half of the colon to the splenic flexure, the author suggests that the diagnosis should be suspected in this condition when the barium sulfate enema reveals no mechanical obstruction¹²¹¹ In a case in which mesenteric arterial occlusion was discovered at operation,¹²¹² the patient recovered after treatment with heparin sodium, the involved segment of bowel was not resected Infarction of the left colon is a rare condition following thrombosis or embolism of the inferior mesenteric vessels, a case is reported in which thrombosis was confined to the intramural vessels of the colon¹²¹³ Three of 4 patients operated on for mesenteric vascular occlusion recovered¹²¹⁴ Descriptions are given of cases of a mesenteric cyst,¹²¹⁵ fibroma¹²¹⁶ and fibroleiomyoma of the mesentery¹²¹⁷

Endometriosis—Two instances of endometriosis of the umbilicus are described¹²¹⁸

Carcinomatous Metastases—In a series of 914 cases of carcinoma in which autopsy was performed,¹²¹⁹ supraclavicular metastases were present in 129, in the latter group, the primary neoplasm was located in the esophagus in approximately 7 per cent, in the stomach in 14 per cent, and in the intestine in 8 per cent In the case of a patient with a seminoma of the testicle and an adenocarcinoma of the ascending colon,¹²²⁰ the peritoneum, omentum, mesenteric lymph nodes, cecum

1211 Harrington, L A Mesenteric Thrombosis, *Am J Roentgenol* **58** 637, 1947

1212 Hendry, W G Superior Mesenteric Arterial Occlusion, *Brit M J* **1** 144, 1948

1213 Thompson, F B Ischemic Infarction of the Left Colon, *Canad M A J* **58** 183, 1948

1214 Ashley, L B, and Benson, C D Mesenteric Vascular Occlusion (Four Resected Cases with Three Recoveries), *Harper Hosp Bull* **5** 159, 1947

1215 Paul, M Mesenteric Cysts, *Brit J Surg* **35** 308, 1948

1216 Nicholas, C P A Case of Fibroma of the Mesentery, *Brit J Surg* **35** 107, 1947

1217 de Nicola, C P, Carpanelli, J B, and Cernich, R Fibroleiomyoma de mesenterio, *Bol y trab, Acad argent de cir* **31** 512, 1947

1218 Weisband, B J, and Monica, C Endometriosis of the Umbilicus, *Am J Surg* **74** 827, 1947

1219 Jakobson, E Ueber die klinische Bedeutung der Untersuchung der supraklavikularen Lymphknoten beim Krebs, *Acta chir Scandinav* **96** 75, 1947

1220 Gagnon, E D An Unusual Case of Multiple Malignancy, *Brit J Surg* **35** 435, 1948

and liver were involved by metastases from the seminoma, the mesenteric lymph nodes, portal vein and liver were involved by metastases from the carcinoma

Adhesions—Administration of heparin sodium in large doses, continued up to seventy-two hours, did not prevent the formation or reformation of intraperitoneal adhesions or the deposition of fibrin on the surface of injured appendixes in rabbits¹²²¹

Acute Porphyrin—A man of 33 was operated on for a suspected perforated ulcer¹⁻²² The large intestine was found to be greatly dilated. Traces of porphyrin later were demonstrated in the urine

1221 Bloor, B M , Dortch, H , Lewis, T H , Kibler, R J , and Shepard, K S The Effect of Heparin upon Intra-Abdominal Adhesions in Rabbits, *Ann Surg* **126** 324, 1947

1222 Dahl, S Acute Porphyrin, *Tidsskr norske lægefor* **67** 157, 1947

News and Comment

GENERAL NEWS

New Journal of Clinical and Laboratory Investigation—The first issue of *The Scandinavian Journal of Clinical and Laboratory Investigation*, a quarterly edited for the Scandinavian Society for Clinical Chemistry and Clinical Physiology, has just appeared. The editors state "The scientific material which will be published in the journal must be closely associated with clinical research and must be based on laboratory investigations. Research executed on the basis of clinical statistics and casuistics will thus fall outside the scope of the journal."

"The journal will also include a short practical section where technical details, short surveys of subjects important from a practical standpoint, description and evaluation of new apparatus will be published."

"It is the hope of the Editorial Board that 'The Scandinavian Journal of Clinical and Laboratory Investigation' will be able to accomplish the task outlined above and in this way help to support the evolution and progress of clinical laboratory activity and assist in the promotion of experimental clinical medicine within the Scandinavian countries."

Manual on the International Exchange of Publications—The United Nations Educational, Scientific and Cultural Organization plans to publish, late in the year, a manual on the international exchange of publications. As an addition to the manual, there will be published a classified list of institutions, including libraries, universities, scientific institutions, learned societies, etc., throughout the world, which are willing to exchange either their own publications or other publications which they have regularly at their disposal.

All institutions which have not sent details of their exchange material to Unesco are urged to communicate before Oct. 1, 1949 with the Unesco Clearing House for Publications, 19 Avenue Kleber, Paris, 16^e, France. The following information should be given: (1) name and full address of the institution; (2) exact titles of the publications offered (actual lists of duplicates offered for exchange are not required, but only a statement that lists of duplicates are available; a catalogue of the institution's own publications available for exchange, or a full bibliographic description of such a catalogue is requested); and (3) conditions of exchange.

Interamerican Review—In accordance with the decision of the Third Interamerican Cardiological Congress, which met in Chicago in June 1948, the Interamerican Cardiological Society is planning the publication of an interamerican review. By means of bilingual abstracts this periodical will provide Latin-American cardiologists with the complete North American cardiovascular literature and, conversely, will keep non-Spanish-speaking cardiologists informed of the South American scientific production in this field.

Book Reviews

Heredity in Human Leukemia and Its Relation to Cancer By Aage Videback, M D Pp 279 Copenhagen Arnold Busck, 1947

The pedigrees of 209 patients with leukemia were examined, and compared with those of a suitable control group of 200 subjects. Among the 4,041 relatives of the leukemic patients there were 17 cases of leukemia and 319 cases of cancer. Among the 3,641 relatives of the controls there were 2 cases of leukemia and 218 cases of cancer. The author concludes that a familial occurrence of leukemia is demonstrated. From statistical studies he states that the "cancer risk" is 31 per cent in relatives of patients with leukemia, as compared with 22 per cent in the control group. This difference is said to be significant. The study offers strong support for the operation of a genetic factor in the etiology of human leukemia. This is of interest because of the undoubted hereditary nature of certain types of animal leukemia.

Diabetic Manual for the Doctor and Patient By Elliott P Joslin, M D, Sc D Eighth edition Price, \$2.50 Pp 260 Philadelphia Lea & Febiger, 1948

When one notes that the present edition of Joslin's Diabetic Manual is the eighth and that the seventh appeared as long ago as 1941, one realizes what a prodigious stretch of time is covered by the whole series. Indeed it is the impression that Dr Joslin was among the first to develop the now generally recognized procedure, as exemplified in this manual, of taking the patient into partnership in understanding his disease, instead of preserving an all-wise aloofness (which at times really masked the ignorance of the physician). Dr Joslin has long since won his fight, even though an occasional diabetic patient is still dismissed by his physician with no other directions than to avoid sweet stuff. But, after all, "nihil agit per saltum." Although fully up to date, the general spirit of the book stays unchanged—the nostalgic Uneeda biscuit (6 Gm) and the 5 cent piece (5 Gm) are still there—but the cut of the famous scales (John Chatillon & Sons, New York) is somewhat darker and less brilliant than in earlier editions. More power to Dr Joslin, whose masterly pen has influenced so effectively the treatment of diabetes in this country! May there be many more editions of this manual in the future.

The Treatment of Malignant Disease by Radium and X-Rays, Being a Practice of Radiotherapy By Ralston Paterson, M C, M D Pp 622 Philadelphia Williams & Wilkins Company, 1948

Dr Paterson is Director of Therapeutic Radiology at the Christie Hospital and Holt Radium Institute in Manchester, England. In his introduction he says that the book is a "practice" of radiotherapy. It is indeed. One would hardly need any other textbook to become a gilt-edged practitioner of radiation therapy. He acknowledges help given by associates. Twelve of the 34 chapters were written by collaborators or with them, notably 55 pages on the breast and uterus by Margaret Tod and 50 pages on the *biologic action of radiation* by Edith Paterson. In a compactly written 18 pages he gives the notions of radiosensitivity and dosage that underlie the treatment policies of his institute, which are then laid

out succinctly in 2 more chapters (27 pages) He denies qualitative superiority of one wavelength over another and will use radium or any kind of roentgen ray to get the irradiation to the tumor He believes that each kind of tumor has its characteristic radiosensitivity, not predictable from Broder's grading of anaplasia

A description of needed equipment is given briefly and definitely, even to number and sizes of radium tubes The author does not insist on voltages above 250 kilovolts even while acknowledging some superiorities Calibration, measurement, calculations, planning, prescribing and achieving the desired tumor dose fill 82 pages of most practical instructions, with depth dose, tables and charts simplified to the essentials He uses only half a dozen qualities of roentgen ray, one tube for each He builds the whole structure on the attainment of the desired tumor dose and mobilizes any amount of effort to achieve it Every patient is measured with the use of roentgenograms and calipers, pointers and protractors Plaster jackets are used whenever needed to assure precision of cross-fire technics, which often make use of multiple fields These are calculated precisely, simultaneous equations being used if necessary to discover the optimum arrangement Examples are worked out Materials and technics for radium molds and roentgen ray beam directors are covered in 15 pages A short chapter deals with reactions The nursing problems are dealt with in later chapters as they arise

The next 17 chapters (306 pages) cover treatment of cancers of the several organs, leading off with 26 pages on the skin The generalizations are careful and the details precise, with sketches, diagrams and roentgenograms and often illustrative calculations The place of surgical treatment is clearly and logically stated The author is more sanguine in regard to radiotherapy of pulmonary and esophageal cancer than most United States authors When irradiation is of no use (as in acute leukemia) or subservient to surgical intervention, this is boldly stated Repeated emphasis is put on the distinction between radical therapy, when there is hope for cure, and treatment for palliation A 3 page chapter deals with causes of failure.

A discussion of telerradium therapy by B W Windeyer and J E Roberts occupies 19 pages, probably more than an American would give it For the protection of the staff from radiation injury the reader is referred to the British Committee Report of 1943, a brief chapter on injury from radium is given, especially concerning physicians and nurses in the operating room

Detailed plans for building, staffing and organization of a radiotherapy institute fill 45 pages, with cuts of forms and examples of clinical, surgical and irradiation records as well as the Institute's schemes for follow-up and statistics Such an institute depends on centralization of therapy for a population of 2,000,000 or more For a smaller lead a radiotherapy department should be included in a general hospital (2 pages)

The last chapter (11 pages) sketches new therapeutic agents, megavolt roentgen rays, multimegavolt betatrons, neutron rays and radioactive isotopes Six charts for radium dosage are designed for cutting out and mounting The index fills 17 columns The illustrations are separately numbered for each chapter, evidently to make future revisions easier

References to some 170 authors are listed at the end of the chapter on biologic effects Other references are given in footnotes all through the text Few errors are noted Small differences from American spelling and usage are unobtrusive except perhaps "radiation" for "irradiation" "Reticuloendothelial tumors" cover lymphoblastoma and more, benign giant cell tumor is "osteoclastoma"

This textbook-handbook has an excellent integration which appeals to this reviewer, who has been aware for some years that young physicians taking up the study of radiology surely needed a modern book covering this field

SYMPTOMS ATTRIBUTABLE TO COLD HEMAGGLUTINATION

Report of Two Cases

JEANNE C BATEMAN, M D *

WASHINGTON, D C

THE PHENOMENON of cold hemagglutination was recognized fifty years ago and gave rise to an extensive foreign literature during the first part of this century. Since its relationship to primary atypical pneumonia was pointed out by Peterson, Ham and Finland,¹ in 1943, the subject has received considerable attention in this country. Whereas cold hemagglutination was originally regarded as a phenomenon of mainly academic interest, it became increasingly evident not only that it was a valuable diagnostic aid in some epidemics of primary atypical pneumonia but that it could give rise to certain definite symptoms occasionally serious in character and directly related to intravascular hemagglutination. Agglutination of all types of red blood cells at cold temperatures by serum, with reversal at warm temperatures, occurs in a wide variety of conditions.² Cold hemagglutination appears to be transient in acute infectious diseases, in trypanosomiasis, in acute hemolytic anemia and in some cases of acquired chronic hemolytic anemia but possibly permanent in cirrhosis of the liver, in Raynaud's syndrome (acrogangrene) and in some cases of acquired chronic hemolytic anemia.^{2b}

The presence of cold hemagglutinins is suspect when there is difficulty in blood-counting procedures or cross matching of blood at room temperatures, or the development of acrocyanosis and hemoglobinuria are noted following exposure to cold. Gangrene of a part may develop if exposure is prolonged.³ Less commonly, thrombotic phenomena are manifest.

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1 Peterson, O L, Ham, T H, and Finland, M. Cold Agglutinins (Auto-hemagglutinins) in Primary Atypical Pneumonias, *Science* **97** 167 (Feb 12) 1943.

2 (a) Finland, M, Peterson, O L, Allen, H E, Samper, B A, and Barnes, M W. Cold Agglutinins. I. Occurrence of Cold Isohemagglutinins in Various Conditions, *J Clin Investigation* **24** 451-457 (July) 1945. (b) Stats, D, and Wasserman, L R. Cold Hemagglutination—an Interpretive Review, *Medicine* **22** 363-424 (Dec) 1943.

3 Stats, D, and Bullowa, J G M. Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities, *Arch Int Med* **72** 506-517 (Oct) 1943.

One of the puzzling but important practical factors in the study of cold hemagglutination is its relationship to thrombotic phenomena and to intravascular hemolysis. Deposition of fibrin and actual thrombus formation probably occur only after prolonged vascular obstruction and stasis resulting from the intravascular agglutination which has been precipitated by the action of the cold hemagglutinins on exposure to cold. Stats⁴ found that blood containing potent cold hemagglutinins was readily hemolyzed when shaken in the cold. Normal blood, with low titers of cold hemagglutinins, was not hemolyzed by shaking. Other authors⁵ also found an apparent increase in mechanical fragility of red blood cells which were subject to cold hemagglutination. The process of agglutination usually seems to change the surface of the blood corpuscles in such a manner that they become more susceptible to the physiologic mechanisms of hemolysis.

Hemolysis in the presence of cold hemagglutinins is unaffected by complement and occurs in heat-inactivated serum, unlike the Donath-Landsteiner phenomenon which requires complement.⁴ Ernstene and Gardner⁶ reported a positive reaction to the Donath-Landsteiner test in the case of a patient who had no history of syphilitic infection but in whom acrocyanosis and hemoglobinuria developed on exposure to cold. After sympathectomy the reaction to the test became negative, the cold hemagglutinin titer being unaltered. A positive reaction to the Donath-Landsteiner test is, however, usually unobtainable for patients with cold hemagglutination which is apparently unrelated to syphilitic infection. It has been suggested⁷ that the same mechanism may be responsible for an elevation of cold hemagglutinin titer and for a seropositive reaction in the absence of syphilis.

The relationship of sulfonamide therapy to intravascular hemolysis in the case of a patient with potent cold hemagglutinins has been thought to be possibly more than casual, yet, it is apparent that the dramatic

4 Stats, D. Cold Hemagglutination and Cold Hemolysis, *J Clin Investigation* **24** 33-42 (Jan) 1945

5 (a) Whittle, C H, Lyell, A, and Gorman, M. Reynaud's Phenomena with Paroxysmal Hemoglobinuria Caused by Cold Hemagglutinins, *Proc Roy Soc Med* **40** 500-502 (July) 1947. (b) Finland, M, Peterson, O L, Allen H E, Samper, B A, and Barnes, M W. Cold Agglutinins. II. Cold Isohemagglutinins in Primary Atypical Pneumonia of Unknown Etiology with a Note on the Occurrence of Hemolytic Anemia in These Cases, *J Clin Investigation* **24** 458-473 (July) 1945.

6 Ernstene, A C, and Gardner, W J. The Effect of Splanchnic Nerve Resection and Sympathetic Ganglionectomy in a Case of Paroxysmal Hemoglobinuria, *J Clin Investigation* **14** 799-805 (Nov) 1935.

7 Lubinski, H, and Goldbloom, A. Acute Hemolytic Anemia Associated with Autoagglutination with a Thermal Amplitude of 0 to 37 C, *Am J Dis Child* **72** 325-335 (Sept) 1946.

incidents of sudden massive hemolysis or thrombosis, now often attributed to sulfonamide therapy, took place before these drugs were used

Data in cases in the literature presenting the symptoms of cold hemagglutinins have been compiled in table 1. These symptoms include acrocyanosis, thrombotic phenomena, hemoglobinuria and/or hemolytic anemia. They may occur separately but are frequently associated. Possible contributing factors are sulfonamide therapy and syphilis.

It will be noted that the majority of cases occur in the third, fourth and fifth decades, with the greatest incidence in the fourth. The greater incidence in males than in females may be partly due to more frequent exposure to cold, with consequent greater likelihood of development of symptoms. A great variance exists in reported titer. It should be remembered that neither the methods used for determination of cold hemagglutination titer nor those for collecting and storing of blood samples are uniform. Atypical pneumonia may be assumed to have been present in more than half these cases. Approximately 1 patient in 4 received sulfonamide therapy. A positive reaction to a blood test for syphilis appears to have been merely coincidental, though the possibility of a "false positive" reaction must be considered. In 42 cases acrocyanosis occurred 13 times, thrombotic phenomena, 6, hemoglobinuria, 12, and various degrees of anemia, 21. Anemia in some cases was extremely sudden in onset and extremely severe in grade. Dramatic hemolytic crises have been reported in cases of primary atypical pneumonia in which the patients did not receive sulfonamide therapy,⁸ in cases of primary atypical pneumonia in which the patients were treated with sulfonamide drugs,⁹ and spontaneously in the case of 1 apparently well person.¹⁰ All these patients presented symptoms which were apparently directly attributable to the presence of cold hemagglutinins.

REPORT OF CASES

Case 1 is an example of vascular occlusion occurring in a case of primary atypical pneumonia accompanied with an elevated cold hemagglutinin titer.

CASE 1—N. O., a bartender of 22, was admitted on Nov. 21, 1945 to the Third Medical Division of Bellevue Hospital with complaints of a chilly feeling, fever,

8 Ginsberg, H. S. Acute Hemolytic Anemia in Primary Atypical Pneumonia Associated with High Titer Cold Agglutinins, *New England J. Med.* **234**: 826-829 (June 20) 1946.

9 (a) Layne, J. A., and Schemm, F. R. Acute Macrocytic Hemolytic Anemia Following Administration of Sulfadiazine, *J. Lab. & Clin. Med.* **29**: 347-351 (April) 1944. (b) Platt, W. R., and Ward, C. S. Cold Isohemagglutinins: Their Association with Hemolytic Anemia and Multiple Thrombosis in Primary Atypical Pneumonia, *Am. J. Clin. Path.* **15**: 202-209 (May) 1945.

10 Currie, J. P. Acute Hemolytic Anemia: Case Presenting Hitherto Unreported Features, *Brit. M. J.* **2**: 8-10 (July 1) 1944.

TABLE 1—Cases Presenting the Symptoms of Cold Hemagglutination

Source	Age	Sex	Race	Highest Cold Agglutinin Titer	Atypical Pneumonia	Sulfonamide Therapy	Arteriosclerosis	Hemolytic Phenomena	Hemoglobinuria	Syphilis	Symptoms	
											Hemoglobin	Hemoglobin Anemia
McCombs, R P, and McElroy, J S Arch Int Med 59 109 117 (Jan 1937)	57	M	W	1 1,024	—	—	—	—	+	—	—	Hemoglobin 10.5 to 11.5 Gm / 100 cc
Peterson, Ham and Finland ¹ Jubinski and Goldbloom ²	11	M	W	1 160 to 1 320 1 4 at room temperature 1 1,024	History suggestive	+	—	—	—	+	—	+
Horstmann, D M, and Tatlock, H J A M A 122 369 370 (June 5) 1943	47	F	W	Pronounced agglutination at room temp	+	—	—	—	+	—	—	+
Hayne and Schemm ^{3a}	36	F	W	—	Broncho pneumonia	+	—	—	—	—	—	+
Finland, Peterson, Allen, Samper and Barnes ^{3b}	35	M	N	1 160	—	—	—	—	—	+	—	+
	45	M	N	1 2,560	—	—	—	—	+	+	—	+
	45	F	W	1 2,560	—	—	—	—	+	—	—	+
	34	M	N	1 80	—	+	—	—	—	—	—	+
Finland, Peterson, Allen, Samper and Barnes ^{2a}	(11 patients)			1 10 to 1 5,130	+	+	—	—	—	—	—	+
Stats and Bullowa ¹	69	M	N	1 3,200	—	—	Arteriosclerosis	—	+	Kahn — Wassermann — Mazzini 2 +	—	Hemoglobin 84 per cent
Platt and Ward ^{4b}	30	F	W	1 256	+	+	—	Multiple severe	+	Kahn —	—	+
Benlans, T H O, and Feasby, W R Lancet 2 479 480 (Oct 25) 1941	52	F	W	1 1,000	—	—	Feet, nose, ears, hands	—	—	—	—	+
												+
Helwig, F O, and Freis, E D J A M A 121 626-628 (Nov 6) 1943	63	F	W	1 4,000 1 1,000	—	—	Nose, ears, hands	—	—	—	—	+
Bonnin, H, Dubarry, J, Dulong de Rosnay, C, and Lucas, P Sang 18-209 280, 1947	46	M	W	1 1,280	Questionable, virus infection	—	Arteriosclerosis	—	—	Kahn —	—	+
Hanns, A Sang 15 506 525, 1942	45	M	W	1 1,000	—	—	Arteriosclerosis, nose	—	+	Wassermann —	—	+
Currie ¹⁰	37	M	W	No titer, clumping at room temp	—	—	—	—	—	Wassermann —	—	+
Le Goff, J M Presse méd 4 628 629 (April 19) 1933	70	M		No titer	—	—	+	+	—	—	—	+
Forbes, G B Brit M J 1 598 600 (May 3) 1947	78	F	M	No titer 1 1 624	—	—	Fingers	—	—	Wassermann —	—	+
Kopplin, F Ztschr f klin Med 1 10 784 788, 1936	75	F		1 712	—	—	Hands, feet, fingers	—	—	—	—	+
Stratton, F Lancet 1 613 614 (May 5) 1943	62	F		1 2 6	—	—	—	—	—	Kahn —	—	+
Ginsberg ⁸	34	M	W	1 2,048	+	—	—	—	—	—	—	+
Ernstene and Gardner ⁹	38	M	W	1 1,280	—	—	Arteriosclerosis, nose, fingers	—	+	Kahn —, Wassermann —	—	+
Whittle, Lyell and Gorman ¹¹	65	F	W	1 2,000,000	—	—	Hands, ears, nose	—	—	Kahn —, Wassermann —	—	+
Case 1	22	M	W	1 2,560	+	—	—	—	—	Wassermann —	—	+
Case 2	43	M	W	1 2 621, 140	—	—	Nose, ears, fingers	—	—	Wassermann —	—	+

^a This patient had pain in the fingers^b This patient had pain in the tips of the extremities

malaise, increasingly severe nonproductive cough and dyspnea. There were moist rhonchi and fine rales in both lung fields. Cultures of the blood and sputum were negative. The white blood cell count was 6,500. On November 25, penicillin therapy was begun and the patient was placed in an oxygen tent. Within twelve hours, signs and symptoms of thrombophlebitis developed in the superficial veins of the right leg. It was noted that the oxygen tent was unusually chilly. The patient gradually recovered. At no time did he receive sulfonamide therapy. The cold hemagglutinin titers were 1:1,280 on November 27, 1:2,560 on December 2 and 1:640 on Jan 10, 1946.

The most curious cases are those in which transient or persistent high titers of cold hemagglutinins suddenly develop from no apparent cause. Case 2 is an example.

CASE 2—M. L., an antique shop proprietor of 43, first experienced purplish blue mottling of the face, ears and fingers after exposure to cold in November 1944. The symptoms were followed by the passage of red urine. The patient's condition was diagnosed as "kidney disease," and he was treated with bed rest for two months. The symptoms reappeared when the patient was permitted to go out of doors but subsided during the following summer, only to reappear with the onset of cold weather. No jaundice was noted. There was no history of primary atypical pneumonia or of other viral infection. Physical examination was essentially non-contributory, except for acrocyanosis following exposure to the cold.

The patient was seen in the spring of 1946 by Dr. Alfred Vogt, of New York, who suspected the presence of cold hemagglutinins and referred him to me for further study.

On April 19, the patient's cold hemagglutination titer, as determined by Kettel's method,^{2b} was 1:2,621,440 against both his own erythrocytes and type O red blood cells. Gross clumping was noted in a specimen of oxalated blood obtained at room temperature. The red cells remained clumped after being removed from the refrigerator and standing at room temperature (23°C) for four hours. Dispersion of erythrocytes took place at incubator temperature.

The patient has been followed at the time of this report for a period of more than two years, during which he has remained in relatively good health. However, with exposure to cool weather there immediately develops bluish purple mottling of the ears, the cheeks, the tip of the nose and the fingers, accompanied with a mild sensation of tingling. About fifteen minutes later, red urine is passed.

The patient was urged to spend his winters in Florida, but this proved impractical, instead, he has consistently protected himself with warm gloves, stockings, etc., during cold weather.

Determinations of cold agglutination titer made at intervals during the two year period are listed in table 2. There has been a wavelike decline in titer with a tendency for the titer to be lowest during the summer. However, the thermal range remains so wide that blood counts are possible only when warm pipets and diluting fluid are used. A mild hypochromic anemia has developed.

On Feb. 10, 1948, salicylate therapy (5.2 Gm. of sodium salicylate daily in divided doses) was begun with the hope of blocking antigen-antibody reaction. At this time the cold agglutinin titer was 1:20,480. On February 17, it was 1:10,240 and the plasma salicylate level was 24.8 mg. per hundred cubic centi-

meters, as determined by the method of Brodie, Udenfriend and Coburn¹¹ The patient continued to show symptoms of acrocyanosis for several days after the institution of therapy Subsidence was difficult to evaluate because of a sudden spell of warm weather Side effects of malaise, ringing in the ears, anorexia and constipation were pronounced The dose of sodium salicylate was reduced to 3.6 Gm

On February 24, the cold agglutinin titer had dropped to 1:2,560, the plasma salicylate level was 230 mg Symptoms of anorexia, malaise and constipation persisted in a milder form

On March 2, the cold agglutinin titer was 1:20,480 Clumping persisted for two hours at room temperature (25 C) up to a dilution of 1:1,280 The plasma salicylate level was 17 mg Since the improvement suggested earlier had not been maintained it was decided to abandon the use of the drug

TABLE 2—Data in Case 2

Date	Titer Cold Hemagglutinins	Plasma Salicylate Level, Mg /100 Cc	Blood Counts
1946			
4/19	1:2,621,440		
6/19	1:327,680		
8/15	1:20,480		
10/7	1:163,840		
1947			
5/22	1:40,960		
1948			
1/7	1:81,920		Hemoglobin 12.4 Gm /100 cc
2/10	1:20,480	0	
2/17	1:10,240	24.8	
2/24	1:2,560	23.0	
3/2	1:20,480	17.0	Hemoglobin 10.77 Gm /100 cc red blood cells 4,880,000 white blood cells 10,450
5/12	1:5,120		
6/8	1:2,560		

Subsequently the cold agglutinin titer fell spontaneously in a manner similar to that noted during previous summers

COMMENT

It is apparent that the primary mechanism responsible for symptoms due to the presence of cold hemagglutinins is intravascular clumping of erythrocytes The precipitating factor is presumably cold, whether due to chilling in an oxygen tent, low outdoor temperature or, possibly, transfusion with chilled blood Stasis then occurs, most apparent in peripheral parts of the body Patchy cyanosis appears but usually subsides when the patient is exposed to a warm temperature However,

11 Brodie, B. B., Udenfriend, S., and Coburn, A. F. The Determination of Salicylic Acid in Plasma, *J. Pharmacol. & Exper. Therap.* **80**: 114-117 (Jan) 1944

by then the tightly clumped erythrocytes have become more fragile than normal and tend to undergo hemolysis when subject to the trauma of circulation. Continued exposure to cold may cause the clumped erythrocytes to impede tissue oxygenation to the point where gangrene will develop in an extremity. This possibility should be considered in cases of bilateral gangrene in which exposure to cold alone has not been of a degree severe enough to produce this pathologic process. Local thrombosis of a deep part is more difficult to explain. The primary mechanism is probably the same. However, before erythrocyte dispersion can take place conversion of the clumped erythrocytes into actual thrombi has taken place with all the known effects of vascular occlusion.

Anemia of either of two types may occur. There may be moderate chronic anemia such as the patient in case 2 exhibited. A probable explanation of this disorder is that repeated bouts of hemolysis are severe enough to raise the hemoglobin content of the blood to a level above the renal threshold. The blood-forming elements, mainly iron, are then lost to the body, and one may expect essentially an iron deficiency anemia which when uncomplicated results in a hypochromic microcytic blood picture. However, owing to the difficulty in making correct blood counts and hematocrit determinations in the presence of potent hemagglutinins, it is difficult or impossible to evaluate the character of the anemia present. Occasionally a hemolytic crisis takes place with a resultant severe anemia. Presumably, sudden severe chilling could initiate such a process, but such a history is rarely, if ever, noted.

Hemoglobinuria results whenever tubular absorption falls behind filtration rate. The red color of the urine voided by these patients is due to the presence of hemoglobin and not to that of free red blood cells.

It is a curious fact that the agglutination titer is not directly related to the type or degree of symptoms. Thermal range is doubtless important, especially in low titer serums.

Only a few cases with extremely high titers of cold hemagglutinins have been reported. Jessen and Bing¹² noted a macroscopic titer of 1:1048,576 and a microscopic titer of 1:33,600,000 in the case of a woman of 69 with Banti's disease. Whittle and others^{5a} reported an instance of a cold hemagglutinin titer of 1:2,000,000 in the case of a woman of 56 with symptoms suggesting Raynaud's disease and with occasional hemoglobinuria. A titer of 1:280,000 was observed by Favour¹³ in a case of terminal myeloid leukemia. Erf¹⁴ reported a

12 Jessen, C. U., and Bing, J. Methods for Differentiating the Cause of Increased Sedimentation Rate, *Acta med. Scandinav.* **105**: 287-300, 1940.

13 Favour, C. B. Autohemagglutinins, *J. Clin. Investigation* **23**: 891-897 (Nov.) 1944.

14 Erf, L. A. A Note on the Stability of Cold Hemagglutinins, *Am. J. Clin. Path.* **15**: 210-213 (May) 1945.

titer of 1 4,194,304 in the case of a man of 24 and one of 1 262 000 in that of a youth of 17, neither of the patients had acrocyanosis, thrombotic phenomena or hemoglobinuria. Erf also mentioned a personal communication from Dameshek regarding a patient with a cold hemagglutinin titer of 1 400,000, but no further details are given.

The use of salicylates was suggested by experimental work on animals and human beings reported in the literature. Swift¹⁵ found that rabbits treated with sodium salicylate per os and at the same time immunized with intravenous injections of bacteria or sheep cells showed diminished complement-fixing antibodies, agglutinins and hemolysins when compared with controls. Anti-Rh-agglutinin formation in guinea pigs and rabbits is reduced when sodium salicylate is administered prior to and during immunization with rhesus monkey blood cells, according to the work of Homburger¹⁶. Jager and Nickerson¹⁷ administered typhoid vaccine to patients receiving massive salicylate therapy, antibody formation was suppressed. Derick and his associates¹⁸ postulated that arthritis from serum sickness was inhibited when circulating antibodies were kept at a low level by the use of antirheumatic drugs, such as neocinchophen and acetylsalicylic acid. The fact that urticaria was not prevented they attributed to the lack of effect of these drugs on sessile antibodies. Neither bacterial sensitivity to a streptococcus nucleoprotein fraction nor the Arthus phenomenon in rabbits was found to be altered by administration of salicylates (Fischel¹⁹). Coburn and Kapp²⁰ demonstrated inhibition of precipitate formation with sodium salicylate in a system containing crystalline egg albumin and its antibody. The immune system became progressively less sensitive to the action of salicylate as the excess of antibody became greater.

The effect of salicylates on the cold hemagglutinin titer in the patient in case 2 was negligible. Two explanations are suggested by the experimental studies of other authors. First, the salicylates were

15 Swift, H. F. The Action of Sodium Salicylate upon the Formation of Immune Bodies, *J. Exper. Med.* **36** 735-760 (Dec.) 1922.

16 Homburger, F. Sodium Salicylate Inhibiting Anti-Rh Immunization in Animals, *Proc. Soc. Exper. Biol. & Med.* **61** 101-102 (Feb.) 1946.

17 Jager, B. V., and Nickerson, M. The Altered Response of Human Beings to the Intramuscular Administration of Typhoid Vaccine During Massive Salicylate Therapy, *Am. J. Med.* **3** 408-422 (Oct.) 1947.

18 Derick, C. L., Hitchcock, C. H., and Swift, H. F. The Effect of Anti-Rheumatic Drugs on the Arthritis and Immune Body Production in Serum Disease, *J. Clin. Investigation* **5** 427-440 (April) 1928.

19 Fischel, E. E. The Effect of Salicylate and Tripeleminamine Hydrochloride on the Arthus Reaction and on Bacterial Allergic Reaction, *Proc. Soc. Exper. Biol. & Med.* **66** 537-541 (Dec.) 1947.

20 Coburn, A. F., and Kapp, E. M. Salicylate Effect on Immune Precipitates, *J. Exper. Med.* **77** 173-183 (Feb.) 1943.

given long after the beginning of antibody formation. Second, the action of salicylates is presumably less effective in the equivalence zone in the region where antibodies are in excess.

SUMMARY AND CONCLUSION

The symptoms of cold hemagglutination include paroxysmal acrocyanosis, thrombotic phenomena, hemoglobinuria and anemia. The primary factor producing most of these phenomena is apparently intravascular clumping initiated by exposure to cold.

Two cases are reported, 1 with very high titer cold hemagglutinins. Salicylate therapy had a negligible effect on the cold hemagglutinin titer and the symptoms in this case.

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ULCER OF THE PYLORIC RING

Report of Twenty Cases

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THE CLINICAL appraisal of ulcerating lesions within the grasp of the pyloric ring is difficult. Such ulcers are relatively rare in individual practice, and in the literature there are only a few widely scattered studies of their significance. The available articles were reviewed as a background for the present analysis of 20 cases of lesion of the pyloric ring for which satisfactory follow-up records were at hand.

SUMMARY OF THE LITERATURE

Butsch,¹ in 1935, summarized the experience at the Mayo Clinic with pyloric lesions. He found reports of 46 cases of pyloric ulcer in the surgical records there. Only 4 lesions had been accurately localized within the ring by roentgenologic studies. Ten lesions had been excised, and each had been found to be benign. In discussing this paper, Eusterman² said (1) that peptic ulcers of the ring are difficult to diagnose in spite of the fact that patients with such lesions usually come to medical attention after a relatively brief course, (2) that such ulcers usually run a stormy course with painful, spastic manifestations, and (3) that they tend to respond poorly to medical management.

Gutman and Hoffman³ reported in 1935 that 41 ulcers of the pyloric ring had been treated in four years in the gastroenterologic service at the Salpêtrière. This number represented about 15 per cent of all cases of peptic ulcers recorded in that service. The authors differentiated juxtapyloric ulcer, ulcer of the pyloric canal and ulcer of the base of the bulb. The differentiation was entirely roentgenologic, as they insisted that accurate localization within the canal was easier for the roentgenologist than for the surgeon. They described considerable variation in the position of the anterior pyloric vein, which is the surgical land-

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1 Butsch, W L. Ulcers of the Pyloric Ring, Proc Staff Meet, Mayo Clin **10** 435-437 (July 10) 1935.

2 Eusterman, G, in discussion on Butsch¹.

3 Gutman, R A, and Hoffman, R. Ulcer of the Pyloric Canal, Arch d mal de l'app digestif **25** 1009-1037 (Dec) 1935.

mark of the sphincter. Sixteen patients in the series had had exploratory operations. In 6 instances, the surgeon had palpated the ulcer in the base of the bulb rather than in the ring.

Gutman and Hoffman asserted that ulcer of the pyloric ring gave rise to "the most variable symptomatology." In 14 of the 41 cases on which they had collected data, there was neither rhythmicity nor periodicity. In spite of the "exposed position" of the ulcer, bouts of pain were of short duration, however, they were of frequent occurrence. Eight patients had coexistent gastric ulcer, 9 had organic pyloric stric-

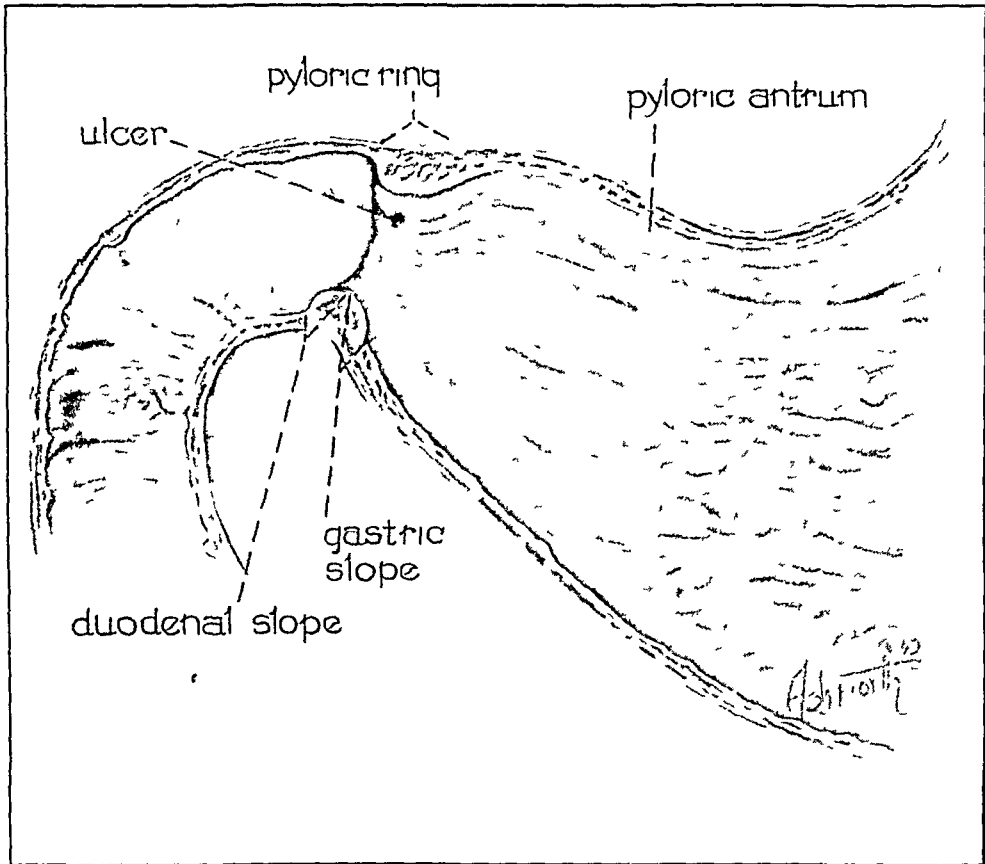


Diagram of the pyloric ring, showing typical location of ulcer

ture, and 9 showed transitory or functional pyloric stricture. The authors recognized the potential malignancy of these lesions but reported no case in which there was a malignant lesion.

J. S. Horsley⁴ in 1936 reported his operative findings in 12 cases of ulcer of the pyloric ring. Three ulcers had caused obstruction, 2 had bled and all were benign.

Jutras,⁵ in 1936, discussed the roentgen diagnosis of pyloric ulcer and concluded that such diagnosis may be most difficult. He called atten-

⁴ Horsley, J. S. Ulcer of the Pyloric Sphincter, *Ann Surg* **103** 738-746 (May) 1936

⁵ Jutras, A. Ulcers of the Pyloric Valve and Canal: Basis for Diagnosis, *Union med du Canada* **65** 660-670 (July) 1936

tion to the false niches produced by the fan-shaped pyloric muscle of Cole. The author's classification for pyloric ulcer according to location, suggested for greater accuracy, was as follows:

Valve (ring)

Gastric slope

Orifice

Duodenal slope

Canal (canal or prepyloric portion)

Lesser curvature

Greater curvature

In 1937, Garen and Bernay,⁶ stimulated by the paper of Gutman and Hoffman, also discussed the roentgen diagnosis of ulcer of the pyloric ring. Their list of pertinent roentgen signs included the following: (1) niche in the ring (such defects are usually small—at most, "several" millimeters in length—and occur on the lesser curvature), (2) elongation and occasional angulation of the pyloric canal with spasm of the canal, and (3) deformity of the antrum adjacent to the ring with roughening of the base of the antrum.

In the experience of Garen and Bernay, stenosis rarely evolved from ulcer of the pyloric ring.

Jensen and Rivers,⁷ in 1939, undertook a comparison of the clinical pictures in 25 cases of benign ulcer and in 25 of antral carcinoma impinging on the ring. They found indistinguishable histories in a third of these cases. After consideration of the histories as well as the roentgen findings, they concluded that one might be confused as to the exact nature of a lesion involving the pyloric ring in about 15 per cent of cases.

The next year, G. W. Horsley⁸ reported 2 cases of benign ulcer of the pyloric sphincter, and Doub⁹ studied 35 cases of true orificial and juxtapyloric ulcers. He excluded from consideration those cases in which "obvious carcinoma" of the antrum was observed on roentgen examination. In the selected group, there were 24 cases of peptic ulcer, 7 cases of antral carcinoma, 3 cases of antral gastritis and 1 case of gastric syphilis. Only 8 of these lesions involved the ring proper, and all 8 were benign peptic ulcers. But it is worthy of comment that 2 ulcers proved to be malignant at operation had been localized by the

6 Garen, C., and Bernay, P. True Pyloric Ulcer. *J. de med. de Lyon* **18** 453-456 (Aug. 20) 1937.

7 Jensen, R. M., and Rivers, A. B. Carcinoma or Ulcer Involving the Pyloric Ring. Differential Diagnosis, *Proc. Staff Meet., Mayo Clin.* **14** 1-4 (Jan. 4) 1939.

8 Horsley, G. W. Ulcers of the Pyloric Sphincter with Case Reports. *Virginia M. Monthly* **67** 29-32 (Jan.) 1940.

9 Doub, H. P. Differential Diagnosis of Pyloric and Prepyloric Ulceration. *Am. J. Roentgenol.* **43** 826-831 (June) 1940.

roentgenologist within the ring, although at gross study they had appeared to be antral in position. Doub concluded that the greatest source of error in the clinical management of ulcers of the pyloric ring lay in the failure of anatomic diagnosis.

Smedal,¹⁰ in 1942, reviewed possible sources of error in the roentgen diagnosis of lesions of the pyloric valve. He stated that accurate diagnosis of the anatomic position was possible and pointed out that the roentgenographic triad of deformity of the base of the cap, a poorly differentiated sphincter and antral spasm usually indicates the presence of an ulcer in the sphincter or on its duodenal slope. Visualization of a collar button-like crater penetrating the sphincter (usually on the side of the lesser curvature) made the diagnosis absolute. Of 10 cases reported by Smedal, the ulcer proved to be benign in 7. In the other 3 cases, the follow-up had not been long enough to prove benignancy.

Tanca Marengo¹¹ reported that there had been 3 cases of ulcer of the pyloric ring among 230 cases of ulcer of the upper gastrointestinal tract recorded over a ten year period. He, too, recognized the difficulty of accurate localization.

REVIEW OF CASES

The present series of 20 cases of ulcer of the pyloric ring was compiled after a review of all cases of peptic ulcer and carcinoma of the gastric antrum reported by a medical group over a twenty year period. Frank carcinomas of the pyloric antrum which had extended into the pyloric ring were excluded from the series.

There were ulcerating lesions of the stomach or duodenum in 28 per cent of all the cases studied by the group. One in every 200 such ulcerating lesions (0.5 per cent) proved to be in the pyloric ring.

The ulceration in the ring was demonstrated by direct visualization at operation in 15 cases and by roentgen examination alone in 5. The pathologic character of each of the 20 lesions was proved by an adequate biopsy, a prolonged follow-up or both. One of the 20 ulcers was malignant.

Fifteen patients were men, and 5 were women. Although their ages ranged from 32 to 77, 15 of the 20 patients were in the fifth or sixth decades.

The duration of symptoms at the time of diagnosis varied from three weeks to twenty years. The average was six and a half years.

In only 11 cases were the clinical symptoms characteristic of "peptic ulcer." Gaseous distress after eating was the predominant

10 Smedal, M. I. Pyloric Ulcers, *Radiology* **39** 200-207 (Aug.) 1942.

11 Tanca Marengo, J. Ulcers of the Pyloric Canal, *An Soc med-quir d Guaymas* **37** 1525-1529 (Jan-March) 1946.

TABLE 1—*Summaries of Reports of 20 Cases*

No	Age and Sex of Patient	Duration of Symptoms at Diag- nosis	Symptoms	Roentgen Observations	Therapy	Surgical and Pathologic Observations	Therapeutic Results	Duration of Follow Up	Roent- gen Evidence of Pyloric Obstruc- tion	Free Gas Accu- mulation at I no De- g (A Ew) Mc
1	51 M	10 yr	Periodic epigastric pain, free period over 6 months	Spastic antrum and bulb pyloric ring deformed with crater, possible carcinoma	Symptomatic medical management		Mild, recurrent dyspepsia, periodic heartburn	12 yr	—	16
2	53 M	9 yr	Periodic epigastric pain, nausea relieved with sodium bicarbonate	Small crater at ring and induration of juxtapyloric walls, suggesting carcinoma	Gastric resection	Benign ulcer in pyloric ring	Patient asymp- tomatic	3 yr	—	10
3	68 M	1 yr	Intermittent burning pain relieved by ingestion of food	Irregular pyloric margins with ulcer in ring, partial pyloric obstruction	Medical management (pro- gressive Sippy treatment)		Minor dyspepsia, no recurrent ulcer pain	7 yr	+	
4	55 M	2 yr	2 episodes epigastric pain, each of 6 months' duration, 1 year free period between	Crater in ring or slightly behind pylorus, distortion of base of bulb	Gastric resection	Benign ulcer in pyloric ring	Patient asymp- tomatic	6 yr	—	
5	55 M	4 mo	Severe gaseous distress and nausea, longest free period, 10 days	Large crater on pyloric sphincter	Gastric resection	Benign ulcer, crater on gas- tric slope of ring admitting fourth finger	Patient asymp- tomatic	15 yr	—	61
6	32 F	8 yr	Irregular vague gaseous dyspepsia, occasional vomiting	Deformity in pylorus with ulcer de- fect	Gastric resection	Benign ulcer in pyloric ring (walls of ring thickened)	Posteibal gaseous dyspepsia relieved by belching	1 yr	—	0
7	60 M	10 yr	Ulcer pain in periods to 4 months, occasional severe crisis of pain and vomiting	Spastic antrum and bulb	Gastric resection	Benign saddle ulcer in pyloric ring	Patient much im- proved, some gaseous dyspepsia	6 mo	—	
8	63 M	18 mo	Ulcer pain and nausea with short free periods	Spastic bulb which could not be filled, spastic antrum	Gastric resection	Benign ulcer in pyloric ring with changes suggesting early adenocarcinoma	Patient asymp- tomatic, died of cerebrovascular accident, no malig- nant growth ob- served at autopsy	2½ yr	+	
9	6, M	3 yr	Periodic epigastric pain, severe ex- acerbation of 3 months' duration just prior to diagnosis	Pylorus thickened and roughened, antrum spastic crater appeared to be in base of bulb	Pylorotomy	Benign ulcer in pyloric ring and on its gastric slope	Patient asymp- tomatic	8 yr	—	18

10	51 M	3 wk	Continuous nausea unrelieved by ingestion of food or sodium bicarbonate	Small crater in pyloric ring and duodenal slope	Gastrectomy	Benign florid ulcer in ring and on its gastric slope, second ulcer on posterior surface of ring	Dumping syndrome	6 yr	—	0,
11	51 M	25 yr *	Typical burning epigastric pain	Small crater determined to be in pyloric ring on side of lesser curvature on repeated studies, antral spasm and deformity of base of bulb	Medical management (progressive Sippy treatment)		Patient asymptomatic	21 yr	—	
12	55 M	9 yr	Recurrent gaseous distress and pressure on heart relieved by belching	Crater in ring, irregular pylorus, thickening of ring	Gastric resection	Benign ulcer, diameter 6 mm, on duodenal slope of ring, ring thickened	Patient asymptomatic	19 yr	—	10,
13	48 F	4 yr	Periodic hunger pain and gaseous distress associated with nausea, lasting to 3 months	Antral spasm, suggestion of crater in pylorus, pyloric obstruction	Gastric resection	Benign ulcer in pyloric ring	Postcibal gaseous distress in lower abdomen	26 yr	+	60,
14	62 F	20 yr	Recurrent epigastric distress with free periods lasting to 2 years	Antral spasm, irregular pyloric canal	Gastric resection	Tumor mass on posterior surface of ring with overlying ulcer that appeared benign on microscopic study	Patient died after 6 months of chronic nephritis, carcinoma in abdominal glands observed at autopsy	6 mo	—	20,
15	55 F	4 yr	Periodic hunger pain relieved with sodium bicarbonate, vomiting	Antral spasm with distorted base of bulb	Gastric resection	Large, indurated, benign ulcer in ring	Patient asymptomatic	22 yr	—	49
16	55 M	10 yr	Recurrent ulcer distress responding temporarily to management, disabling pain and vomiting for 6 months prior to operation	Deformity of base of bulb with crater in ring	Gastric resection	Benign ulcer in ring	Patient asymptomatic	3 mo	+	4
17	53 M	9 yr	Periodic epigastric distress and fullness relieved with sodium bicarbonate, occasional nausea	Small crater at gastric side of pyloric ring	Subtotal gastrectomy	Ulcer, diameter 8 mm, at junction of pylorus and duodenum, active benign ulcer in ring	Patient asymptomatic	5 yr	—	10
18	77 F	8 yr	Occasional distress 2 to 3 hr after eating relieved with sodium bicarbonate	Small crater in pyloric ring, second ulcer on lesser curvature	Medical management (progressive Sippy treatment)		Occasional localized pain and nausea	17 mo	—	10
19	45 F	10 yr	Recurrent, severe vomiting relieved by ingestion of sodium bicarbonate or food, dull, diffuse epigastric pain, nonrhythmic during these episodes	Pylorospasm with ulcer involving pyloric ring, no retention at time of examination	Medical management		Recurrent periodic vomiting	1½ yr	+	62
20	58 F	3 yr	Monthly episodes epigastric pain and nausea of 3 to 4 days' duration, no relief with food	Persistent narrowing of pyloric canal, deformity of base of bulb	Gastrectomy	Benign ulcer, diameter 2.0 cm, of pyloric ring and its gastric slope	Patient asymptomatic	6 mo	—	10

* Recurrent ulcer pain and two hemorrhages occurred twenty five years prior to recorded episode, which was of three months' duration

symptom in 7 cases. Nausea was a complaint in 10. In 4, obstructive symptoms were present from time to time. However, in no case was there cicatricial pyloric stricture. Crisis-like pain and vomiting were present in 1 case.

Values for gastric acidity, when reported, tended to be in the lower normal range.

Accurate roentgen localization of crater of the pyloric ring was made in 12 cases. In 5 others, craters localized close to, but not in, the ring on roentgen examination proved at operation to be in the ring. Antral spasm was noted on fluoroscopic examination in 8 cases and spasm of the bulb in 7. In 2 cases, there was a significant, four hour, retention of barium sulfate.

Ten of the 15 patients who had been operated on reported themselves subsequently asymptomatic. Four reported nonincapacitating or minor postcibal fulness and distress. An annoying dumping syndrome characterized by postcibal distress, weakness, nausea and sweating developed in 1 case.

Of the 5 patients who elected medical management, 2 had recurrence of the ulcer distress on breaking the therapeutic routine. Two have gone seven and twelve years, respectively, at the time of writing without incapacitating or severe recurrence of the ulcer. One patient has remained free of recurrence for over twenty-one years.

COMMENT

It has been shown repeatedly that prepyloric ulcer tends, except in the presence of a second duodenal ulcer, to be malignant. This fact has colored the physician's diagnostic thinking about ulcer of the pyloric ring. In pointing out the high incidence of carcinoma in the prepyloric portion of the stomach, Holmes and Hampton¹² in 1932 carefully excluded from consideration those lesions involving the pyloric ring. Indeed, a review of the reported cases and the observations in the present series show that malignant ulcer within the ring is rare, benign ulcer is the rule. When direct visualization or roentgenographic examination shows a crater involving the pyloric ring, the chance of the lesion's being malignant is relatively small. Other factors may be considered in selecting the method of management.

The clinical value of this information, however, depends on the accurate localization of ulcers of the ring. Since no significant symptom complex characterizes localization in the ring, the roentgenographic evidence becomes of first importance. The demonstration of a crater in the ring should be attempted by fluoroscopic and roentgenographic

12 Holmes, G. W. and Hampton, A. O. The Incidence of Carcinoma in Certain Chronic Ulcerating Lesions of the Stomach, *J. A. M. A.* 99:905-908 (Sept 10) 1932.

examination In the absence of a demonstrable crater, the significant roentgenographic triad of antral spasm, a poorly differentiated ring and deformity of the bulb should be recognized That such a complex indicates the presence of an ulcer in the ring or on its duodenal slope is borne out by the data in the present series Seven of the patients showing this roentgenographic triad were found at operation to have craters of the ring When the decision is difficult, a period of carefully controlled medical management may permit clarification of the roentgen signs

The results of surgical therapy must be considered good However, 5 of the 15 patients operated on continued to have dyspepsia, though in each case to a much lower degree than before the operation It should be emphasized that their cases do not represent failures of medical management Ten of the patients were operated on under the impression that ulcer of the ring was probably malignant, and 5 were operated on with the incorrect diagnosis of prepyloric ulcer Only 3 of the 5 patients managed medically had results which could be considered good, these 3 patients have gone for many years at the time of this report without complications or noteworthy incapacity

SUMMARY AND CONCLUSIONS

The literature concerning ulcer of the pyloric ring is reviewed

Twenty cases of an ulcerating lesion in the pyloric ring are reported

No characteristic symptom complex has emerged to permit accurate localization of an ulcer in the pyloric ring

The accurate roentgenographic localization of many lesions of the ring is possible with the aid of Smedal's¹⁰ roentgenographic triad (deformity of the base of the cap, a poorly differentiated sphincter and antral spasm)

The incidence of carcinoma in ulcer of the pyloric ring is relatively low

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SPONTANEOUS RUPTURE OF SYPHILITIC SACCULAR ANEURYSMS OF THE ASCENDING AORTA INTO THE PERICARDIAL CAVITY, WITH HEMOPERICARDIUM

Report of Sudden Death in Twenty-Nine Cases

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NEW YORK

THIS REPORT deals with sudden and unexpected natural death in 29 cases in which the cause of death was spontaneous rupture of a saccular aneurysm of the intrapericardial portion of the ascending aorta into the pericardial cavity, with resultant hemopericardium and cardiac tamponade

The pathologist, in performing an autopsy, attempts to determine the cause of death. One of the least difficult diagnoses is that of a large hemorrhage into the pericardial cavity. If the pericardium is healthy, the hemorrhage may occur in various ways: (a) from spontaneous rupture of the heart wall, from chronic cardiac aneurysm or from necrosis of the myocardium after occlusion of a coronary artery, (b) from rupture of a dissecting aneurysm of the aorta into the pericardial cavity, (c) from an aneurysm of the otherwise normal coronary artery or of the pulmonary artery or from rupture of an atheromatous coronary artery, (d) from trauma, such as bullet and stab wounds of the pericardium and heart, traumatic cardiac rupture due to direct injury, bone fracture or compression, other forms of trauma, and (in true rupture) either internal pressure or tearing, and (e) from rupture of a syphilitic saccular aneurysm of the ascending aorta, lying within the pericardial cavity or eroding into the pericardial cavity.

SOURCE OF MATERIAL

The Office of the Chief Medical Examiner of the city of New York, from whose files these case records were selected, is called on to investigate approximately 16,000 deaths each year¹. This figure represents about 20 per cent of all deaths occurring in the city of New York, of these, about 50 per cent are due to natural

From the Office of the Chief Medical Examiner, City of New York.

¹ Annual Statistical Reports of the Office of the Chief Medical Examiner, New York.

causes The law requires that sudden, unexpected or unusual deaths be reported to the medical examiner's office for investigation² "Natural death" indicates that trauma played no part in the causation

Autopsies were performed in only 16 per cent of natural deaths recorded, as compared with 25 per cent of all deaths¹ The latter percentage was higher because of the mandatory performance of necropsy in violent or traumatic deaths

Helpern and Rabson,³ in a study of the records of the Office of the Chief Medical Examiner of 2,030 sudden and unexpected natural deaths in which an autopsy was performed in the Borough of Manhattan from Jan 1, 1937, to June 30, 1943, noted that death was due to disorders of the heart and aorta in 912 cases (44.9 per cent) Syphilitic aortitis, complicated by aneurysm, occlusion of coronary ostiums or aortic valvular insufficiency, occurred in 107 cases, or 11.7 per cent of the deaths due to disorders of the heart and aorta and 5.3 per cent of the total of 2,030 deaths

PATHOLOGY

The pathology of syphilitic aortitis has been described by various authors⁴ All were essentially in agreement as to the gross and microscopic appearance of the lesions in syphilitic aortitis

The earliest lesions occur in the adventitia of the root of the aorta About the vasa vasorum, a collection of round cells appears, including lymphocytes and plasma cells Small miliary gummas may be formed Obliterating endarteritis of the vasa vasorum takes place Some of the vasa vasorum extend into the media, where their growth is associated with obliterating endarteritis, destruction of the elastic tissue, forma-

² New York City Charter 1901, sect 1570 and 1751, as added by L 1915, ch 284, sect 2

³ Helpern, M, and Rabson, M S Sudden and Unexpected Natural Death—General Considerations and Statistics, New York State J Med **45** 1197, 1945

⁴ (a) Leary, T Syphilitic Aortitis as a Cause of Sudden Death, New England J Med **223** 789, 1940 (b) Leary, T, and Wearn, J T Two Cases of Complete Occlusion of Both Coronary Orifices, Am Heart J **5** 412, 1930 (c) Berk, L H Cardiovascular Syphilis, New York State J Med **41** 223, 1941 (d) Maitland, H S Syphilis of the Aorta and Heart, Am Heart J **6** 1, 1930, (e) Pathology of Syphilis with Special Reference to the Development of Luetic Aortitis, Bull New York Acad Med **8** 451, 1932 (f) McDonald, S, Jr Syphilitic Aortitis in Young Adults with Special Reference to a Congenital Etiology, Brit J Ven Dis **10** 183, 1934 (g) Saphir, O, and Scott, R W Observations on One Hundred and Seven Cases of Syphilitic Aortic Insufficiency with Special Reference to Aortic Valve Areas, Myocardium and Branches of the Aorta, Am Heart J **6** 56, 1930, (h) Involvement of the Aortic Valve in Syphilitic Aortitis, Am J Path **3** 527, 1927 (i) Scott, R W Syphilitic Aortic Insufficiency, Arch Int Med **34** 645 (Nov) 1924 (j) Warr, O S Syphilis of the Heart and Aorta—A Report of One Hundred Cases with Autopsy Findings, South M J **25** 711, 1932

tion of gummas and development of fibroblastic tissue. As a result of the diffuse destruction of the media, the aorta dilates because the weakened, nonelastic aorta cannot resist the sustained intra-aortic pressure. If the destruction of the media is localized aneurysms may develop. These are saccular in the localized forms, but diffusely fusiform if the destruction is more extensive. Unless aortic insufficiency or atresia of the ostiums of the coronary vessels is present, an aneurysm has little effect on the heart. The intima becomes greatly thickened. The wall of the aorta, on cross section through the areas of syphilitic involvement, may be seen to be thickened.

The gross appearance of the syphilitic aorta is characteristic. The intima has lost its smooth appearance, showing irregular, longitudinal wrinkling, or "tree barking" the effect of the underlying areas of inflammatory fibrosis in the media, which causes the elevations and depressions seen in the intima. Thickened, pearl gray plaques are present, which in early lesions are sharply outlined, elevated and translucent. As the lesion becomes older these plaques tend to spread, so that the entire intimal surface becomes irregular, with pitting and scarring.

The root of the aorta at its origin is by far the commonest place of involvement, because of the rich supply of vasa vasorum in that region.^{4b} Sites in order of decreasing frequency are the ascending aorta, the arch, the descending aorta and, last, the abdominal aorta.⁵

The earliest lesion that can be seen grossly is located just above the commissures distal to the attachment of the aortic cusps. The lesion is pearl gray, raised, has a sharp outline and, as Martland has described it,^{4d,e} is roughly triangular, the base of the triangle pointing upward in the direction of the length of the aorta. The early plaque may be the only evidence of syphilis at autopsy, or, from such a plaque in the root, the process may spread horizontally so as to encircle completely the root of the aorta (this condition is sometimes called the girdle of Venus). The process may spread up the ascending aorta to the origins of the great vessels arising from the aortic arch, continuing up these vessels or causing a narrowing of their mouths. From the arch the process then may extend into the thoracic aorta.

Separation of the aortic commissures occurs when the syphilitic process in the root of the aorta continues downward, in the line of least resistance, between the attachments of the aortic cusps. In the commissure one may find a thickened, longitudinal, raised area separating the attachments of the cusps. As a result of the separation, dilation of

5 Willius, F. A. Newer Concepts of Cardiovascular Syphilis, *Tennessee M. A.* **27** 494, 1934, *Cardiac Clinics*, Clinic on Syphilitic Aortitis with Aortic Insufficiency, Cardiac Hypertrophy with Congestive Failure, *Proc. Staff Meet., Mayo Clin.* **10** 505, 1935.

the aortic ring takes place, causing an aortic insufficiency. The free edges of the aortic cusps may be thickened and rolled, this is not primarily an organic change but, rather, a functional one, due to the mechanical effect of the aortic insufficiency. Just below the aortic cusps and on the posterior wall of the left ventricle are false valves due to endocardial reduplication, which, in turn, is a result of the passage of blood back into the left ventricle due to the aortic insufficiency. The syphilitic involvement at the root of the aorta may cause an increase in the circumference of the aorta, just above the free margins of the cusps. This dilatation may be sufficient to cause an insufficiency of the aortic ring, even though the syphilitic process has not extended downward to the commissures so as to separate the cusps. The aortic insufficiency, if it develops early, before dilatation of the aorta, may at times prevent the formation of aneurysm by relieving intra-aortic pressure. However, aortic insufficiency may occur after the development of aneurysmal dilatation of the aorta if the syphilitic process then extends down to the commissures.

Anatomically, it is of interest to note that the root of the aorta lies within the pericardial reflection. It is also to be noted that syphilis of the aorta occurs most commonly in the root of the aorta, which therefore is the region of oldest syphilitic involvement. The intrathoracic pressure is also greatest in the first part of the aorta. It is therefore not surprising to observe either a small saccular aneurysm which has ruptured into the pericardial cavity or a dissecting aneurysm which, unable to dissect upward because of the scarring of the media, ruptures through the adventitia and into the pericardial cavity. Either condition may lead to sudden death by causing tamponade.

The frequent coexistence of syphilis of the ascending aorta and atheromatosis has been noted by many pathologists. It is only in the older age groups that one finds arteriosclerotic changes in the ascending aorta, and these never progress to the extent to which they are found in syphilis. This is more than coincidence. Syphilis of the ascending aorta, if of sufficient duration, predisposes to associated atheromatosis, with its characteristic yellow plaques, hyaline and fatty atheromatous ulcers and calcification.⁶

REPORT OF CASES

CASE 1—W. L., a white man aged 45, became ill at his place of employment and died in a few minutes, on July 5, 1938. Cause of death was spontaneous rupture of a saccular aortic aneurysm. Other findings were intrapericardial hemorrhage and syphilitic aortitis.

⁶ Leary,^{4a} Beik,^{4c} Gordon, W. H., Parker, F., Jr., and Weiss, S. Gummatous Aortitis, *Arch. Int. Med.* **70**: 396 (Sept.) 1942. Jensen, J. Cardiovascular Syphilis, *Urol. & Cutan. Rev.* **46**: 152, 1942. Smith, A. L. Mesaortitis. Its Pathology and Diagnosis, *ibid.* **46**: 156, 1942.

CASE 6—J J, a white man aged 55, was found dead in bed in his rooming house, on April 15, 1939. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible. The mouths of the coronary arteries were patent. On section the coronary arteries were observed to be patent, showing only slight sclerosis. The myocardium appeared normal. A large aneurysm of the ascending aorta extended up to the aortic arch, the aneurysm was $5\frac{5}{8}$ inches (14 cm) in circumference. The ascending aorta and the lining of the aneurysm showed yellowish and pearl gray plaques, atheromatous plaques, a few of which showed superficial ulceration, were intermingled. A T-shaped rupture of the aneurysm was located just within the reflection of the pericardium on the aorta anteriorly.

CASE 7—W R, a Negro aged 43, had been in apparently good health but collapsed on the street and died almost immediately, on June 5, 1939. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 575 Gm. Hypertrophy and dilatation of the left ventricle were present. The pericardial cavity was filled with fluid and some clotted blood, which completely surrounded the heart. The aortic valve was dilated because of a separation of the commissures by thickened, pearl gray plaques, which extended upward and to each side of the commissures. The aorta was thickened by characteristic pearl gray plaques, with longitudinal wrinkling. Between the plaques were yellow sclerotic plaques and some calcification. The mouths of the coronary arteries were involved in the syphilitic process and were smaller than normal. On section the coronary arteries showed a moderate grade of sclerosis, the lumen was narrowed, but not obstructed. The myocardium showed a few fibrous patches. There was a small saccular aneurysm of the ascending aorta, located $\frac{1}{2}$ inch (1.2 cm) above the commissure separating the noncoronary from the right coronary cusp. The aneurysm, $\frac{1}{2}$ inch (1.2 cm) in diameter and $\frac{1}{2}$ inch in depth, was thinned out, in its center was a perforation about $\frac{1}{8}$ inch (0.3 cm) in diameter, opening into the pericardial cavity. The rest of the aorta showed some sclerosis and a few pearl gray longitudinal plaques.

CASE 8—S B, a Negro aged 41, was found dead in his bed on June 25, 1939. According to relatives, he had complained of being ill shortly before his death. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were tamponade of the heart, chronic syphilitic aortitis and chronic rheumatic valvular disease, affecting the mitral and aortic valves. The results of Kline diagnostic and exclusion tests were positive.

Necropsy—The heart weighed 500 Gm. Slight hypertrophy of the left ventricle was noted. The pericardial cavity was distended with 550 cc of fluid and clotted blood, tamponading the heart. The tricuspid and pulmonary valves were normal. The leaflets of the mitral valve showed fibrous thickening, especially along the line of closure, with evidence of vascularization, slight thickening of the chordae tendineae had taken place. The cusps of the aortic valve were thickened, with small, ridgelike scars along the line of closure. The aortic ring was $3\frac{1}{4}$ inches

(8 cm) in circumference. The ascending aorta, the arch and the descending aorta showed uneven thickening, puckering and wrinkling, a few small atheromatous plaques were intermingled. Thickening of the aorta had taken place along the commissures between the cusps, but the syphilitic process had not spread down so as to separate the commissures. A small saccular aneurysm was located $\frac{1}{4}$ inch (0.6 cm) above the commissure between the right anterior and the posterior cusp, it was $\frac{3}{8}$ inch (0.9 cm) in diameter and $\frac{3}{8}$ inch in depth, and its external surface was the adventitia on the anterior surface of the aorta, which was just adjacent to the appendage of the left atrium. A $\frac{1}{8}$ inch (0.3 cm) rupture, on the surface of the aneurysm, opened into the pericardial cavity. The mouths of the coronary arteries were patent except for a slight narrowing of the mouth of the right coronary artery. The coronary arteries showed a moderate amount of sclerosis. The myocardium appeared normal, on section, no lesions were observed.

CASE 9—L. S., a white man aged 43, died Jan. 30, 1941. He was said to have fallen suddenly to the ground while unloading bags of cement from a truck. He died almost immediately. Cause of death was spontaneous rupture of an aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 300 Gm. The pericardial cavity was distended with fluid and clotted blood. Above the pericardial sac was an aneurysm of the ascending aorta and the arch of the aorta. The dilatation began $1\frac{1}{2}$ inches (3.7 cm) above the aortic valves, it then formed a large saccular aneurysm of the aorta $2\frac{1}{2}$ inches (6.2 cm) in length. The aneurysm was thin walled and about the size of an orange, it lay behind the heart and was in contact with the pericardial sac, just above and posterior to the right atrium. The aneurysm had ruptured through a tear in the aorta, $\frac{1}{2}$ inch (1.2 cm) in diameter, and had torn a $\frac{1}{2}$ inch opening in the pericardial cavity, so that from the inner surface of the pericardial cavity a direct communication had been established with the inner surface of the aneurysm. The cavity of the aneurysm, in addition to the syphilitic process, showed extensive atherosclerosis, with calcification in spots and some friable thrombus material. The remainder of the ascending aorta showed a syphilitic process combined with atheroma, which extended throughout the rest of the aorta, ending 3 inches (7.5 cm) above the bifurcation of the abdominal aorta. The valves of the heart were normal and flexible. The aortic valve was normal. The mouths of the coronary arteries were not involved in the syphilitic process. The coronary arteries showed moderate atherosclerosis, but the lumen was patent throughout. The myocardium appeared to be normal and showed no lesions.

CASE 10—H. S., a Negro woman aged 42, became ill suddenly while traveling in a bus, collapsed and died in a few minutes, on Feb. 19, 1941. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, causing a complete tamponade of the heart. The valves of the heart were normal and flexible. The ascending aorta was the seat of a syphilitic process with pearl gray plaques and longitudinal wrinkling, the lesion did not, however, involve the mouths of the coronary arteries. On section the coronary arteries were observed to be normal. The myocardium showed no lesions. A saccular aneurysm of the ascending aorta was situated about $\frac{3}{4}$ inch

(1.8 cm) above the aortic valves on the anterior surface, just to the right of the pulmonary artery. The aneurysm was 1 inch (2.5 cm) in diameter, there was a $\frac{1}{4}$ inch (0.6 cm) rupture in it, adjacent to the pulmonary artery.

CASE 11—M. G., a Negro woman aged 38, died April 7, 1941. She collapsed while at home talking to members of her family and died in a short time. The family stated that she had not been ill before. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 370 Gm. The pericardial cavity was filled with fluid blood, which compressed the heart. The valves were normal and flexible. The ascending aorta showed a syphilitic aortitis, with pearl gray plaques and longitudinal wrinkling. The opening of the right coronary artery was almost completely obliterated by the syphilitic process, that of the left artery was only slightly involved, but was patent. The coronary arteries showed no lesions on section. The myocardium was normal. Situated between the right coronary and the noncoronary cusp, and about $\frac{1}{2}$ inch (1.2 cm) above the latter, was a small aneurysm, with thinned-out walls and measuring $\frac{1}{4}$ inch (0.6 cm) in diameter, in the center of which was a $\frac{1}{8}$ inch (0.3 cm) perforation opening into the pericardial cavity.

CASE 12—R. B., a Negro aged 35, died Jan. 5, 1942. He was known to be diabetic. He was found lying on the floor at his place of employment by a fellow employee. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which compressed the heart from all sides. The valves of the heart were normal and flexible. The mouths of the coronary arteries were only slightly encroached on by the syphilitic process in the aorta and were not narrowed. On section the coronary arteries showed no lesions. The myocardium was normal. The ascending aorta showed pearl gray plaques and longitudinal wrinkling. On the posterior wall of the aorta, about $\frac{3}{4}$ inch (1.8 cm) above the right coronary and the noncoronary cusp, was a saccular aneurysm, 1 inch (2.5 cm) in diameter, a small perforation, $\frac{1}{8}$ inch (0.3 cm) in diameter, was present in the depth of the aneurysm opening into the pericardial cavity.

CASE 13—G. C., a Negro aged 43, was said to have had a heart attack on Jan. 12, 1942, he was treated by a physician, who advised him to stay in bed for a week. On January 15, while at work, he became ill. When an ambulance surgeon arrived, the patient was in coma, perspiring and breathing slowly. He came out of the coma and became maniacal, and the surgeon administered $\frac{1}{4}$ grain of morphine sulfate. The patient quieted down, while en route to the hospital his respiration again became slow, and he died in the ambulance. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta with rupture into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was enlarged. It was adherent to the chest wall by fibrous adhesions, especially near the conus arteriosus. The pericardial cavity was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible with the exception of the aortic valve, which showed some separation at all the commissures. There was a syphilitic process of the ascending aorta, which also encroached on the mouths of

the right and left coronary arteries, narrowing them. The coronary arteries showed a slight amount of sclerosis on section. A few fibrous patches were scattered throughout the myocardium. An aneurysm of the ascending aorta, beginning 1 inch (2.5 cm) above the valves, was of considerable size and irregularly saccular. A point of rupture, about $\frac{1}{2}$ inch (1.2 cm) in length and situated at the junction of the aorta and the conus arteriosus, opened directly into the pericardial cavity.

CASE 15—J. R., a white man aged 42, was found dead sitting on the stairs of his residence, on Feb. 17, 1942. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was enlarged. The pericardial cavity was distended with fluid and clotted blood, causing a tamponade of the heart. The valves of the heart were normal and flexible. The aortic valve appeared normal, although the aortic ring was somewhat dilated by the syphilitic process, which commenced just above the cusps. The mouths of both coronary arteries were encroached on and narrowed, but not occluded. An aneurysm of the ascending aorta, located just above the junction of the noncoronary cusp and the left coronary cusp, was about $1\frac{3}{4}$ inches (4.3 cm) across the opening and about $1\frac{3}{4}$ inches in depth. It had thinned-out walls. There was a stellate perforation, $\frac{1}{8}$ inch (0.3 cm) in diameter, in the wall of the aneurysm, which opened directly into the pericardial cavity. The ascending aorta showed rugose, grayish and yellowish plaques and longitudinal wrinkling. On section the coronary arteries appeared moderately sclerotic, but they were patent throughout. The myocardium showed a few fibrous streaks.

CASE 16—C. N., an Oriental man aged 45, was found lying dead on the floor of his residence on April 24, 1942. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which had compressed the heart. The valves were normal and flexible. The mouths of the coronary arteries were of normal caliber. On section the coronary arteries were observed to be normal. The myocardium showed no lesions. The ascending aorta showed pearl gray plaques with longitudinal wrinkling. There was a large saccular aneurysm of the ascending aorta, which had emerged from the pericardial sac. Near the point of emergence of the aorta, the aneurysm had eroded back into the pericardial cavity, into which it had ruptured directly.

CASE 17—E. Q., a Negro woman aged 49, collapsed while working as a laundress and died almost at once, on June 9, 1942. Her family stated that she had previously been in good health. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 300 Gm. The pericardial sac was distended by fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart, including the aortic valve, were normal and flexible. There was slight separation of the commissure between the posterior and the right coronary cusp. The mouths of the coronary arteries were not involved. On section the coronary arteries were seen to be normal and patent. The myocardium showed no lesions. The intimal lining of the ascending aorta was extensively wrinkled, presenting a typical "tree bark" appearance, with pearl gray plaques.

The syphilitic process extended as far up as the isthmus of the aorta. There was a small saccular aneurysm of the ascending aorta, its lower margin was situated $\frac{1}{4}$ inch (0.6 cm) above the commissure between the posterior and the right anterior cusp. The aneurysm lay just adjacent to, and was overlapped by, the left atrial appendage. An $\frac{1}{8}$ inch (0.3 cm) perforation of the aneurysm was situated $\frac{3}{4}$ inch (1.8 cm) above the sulcus, between the aorta and the right ventricle and ruptured directly into the pericardial cavity. The aneurysm was 1 inch (2.5 cm) in diameter, was circular and had $\frac{1}{2}$ inch (1.2 cm) opening in the ascending aorta.

CASE 18—L. B., a Negro aged 38, was found lying dead in his bunk aboard a steamship on Dec. 9, 1942. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 500 Gm and showed hypertrophy of the left ventricle. The pericardial sac was distended with clotted blood, causing a tamponade of the heart. The valves of the heart were normal and flexible. There was no separation of the commissures of the aortic cusps. There was slight dilatation of the aortic ring, which was 3 inches (7.5 cm) in circumference. The mouths of the coronary arteries were patent. The syphilitic aortitis did not encroach on the aortic valve or on the mouths of the coronary arteries. The coronary vessels showed slight atherosclerosis. The myocardium was brown and showed no lesions. The ascending aorta, the arch and the descending aorta, almost to the diaphragm, presented a characteristic wrinkled, puckered and scarred appearance resembling the bark of a tree, with pearl gray plaques. There was a small saccular aneurysm just above the left anterior cusp of the aortic valve, it was $\frac{5}{8}$ inch (1.5 cm) in diameter. A small rupture of the aneurysm, $\frac{1}{8}$ inch (0.3 cm) in diameter, was situated between the commissure of the posterior and left anterior cusp and the mouth of the left coronary artery, it entered the pericardial cavity $\frac{1}{2}$ inch (1.2 cm) above the left atrial appendage, on the posterior surface of the ascending aorta.

CASE 19—W. B., a Negro aged 47, was suddenly taken ill, collapsed and died on a sidewalk, on Jan. 27, 1943. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 400 Gm. The pericardial sac was distended with clotted blood, causing a complete tamponade of the heart. The valves of the heart were normal and flexible. There was no separation of the commissures of the aortic cusps. The ascending aorta showed a syphilitic process with pearl gray plaques, a "tree bark" appearance and longitudinal wrinkling, this process extended through the entire aorta to the descending aorta. A saccular aneurysm of the ascending aorta located $\frac{3}{4}$ inch (1.8 cm) above the cusps and measuring 1 inch (2.5 cm) in diameter, contained a $\frac{1}{4}$ inch (0.6 cm) rupture in its center, opening directly into the pericardial cavity. The mouths of the coronary arteries were patent and were not encroached on by the syphilitic process. On section the coronary arteries showed slight sclerosis, but no obstruction. The myocardium showed no lesions.

CASE 20—A. K., a white man aged 65 years, was found lying dead on the floor of the bathroom at his residence, on Aug. 2, 1943. Cause of death was spontaneous rupture of a large saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The valves were normal and flexible. The pericardial sac was distended with fluid and clotted blood, which had caused a tamponade of the heart. A large saccular aneurysm of the ascending aorta had eroded the posterior surface of the manubrium and the upper part of the body of the sternum. This aneurysm filled the superior mediastinum, it was $4\frac{1}{2}$ inches (11.2 cm) in diameter and lined with laminated clot, and its wall was calcified. A rupture $\frac{1}{2}$ inch (1.2 cm) in diameter, in the intrapericardial portion of the ascending aorta, opened directly into the pericardial sac. The syphilitic process encroached on, but did not narrow, the mouths of the coronary arteries. On section the coronary arteries showed slight sclerosis, but the myocardium showed no lesions.

CASE 21—L. A., a Negro woman aged 38, died Dec. 14, 1943. She was found dead on the floor of her apartment by her husband, who stated that she had not been ill before. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 440 Gm. The pericardial cavity was filled with fluid and clotted blood, completely compressing the heart. The valves of the heart were normal and flexible. The mouths of the coronary arteries were slightly encroached on by the syphilitic process. The coronary arteries were normal on section. The myocardium showed no lesions. The ascending aorta showed a syphilitic process with "tree bark" appearance and pearl gray plaques. Three aneurysms of the ascending aorta were located just above the aortic valve and were from about $\frac{1}{4}$ inch (0.6 cm) to 1 inch (2.5 cm) in diameter. The largest showed 1 mm perforation, located in its upper portion and opening directly into the pericardial cavity.

CASE 22—An unknown Negro, about 38 years of age, collapsed on the street and died in a few minutes, on March 3, 1944. Cause of death was spontaneous rupture of a large saccular aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was not enlarged. The pericardial sac was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible. The aortic valve cusps were not encroached on by the syphilitic aortitis, nor were the mouths of the coronary arteries. The coronary arteries showed no lesions on section. The myocardium was normal. The ascending aorta was slightly dilated. The wall was thickened and the intimal surface somewhat corrugated. An extensively scarred and thickened area lay in the ascending aorta, just above the commissure between the right and the left anterior cusp. This wrinkled, corrugated plaque was also somewhat calcified. There were wrinkling and corrugation of the aorta just above the posterior cusp. The remainder of the ascending aorta was fairly smooth, although thickened, and the adventitia was definitely thickened and fibrous. In the arch of the aorta was a $1\frac{5}{8}$ inch (4 cm) saccular aneurysm, directed upward and backward against the anterior surface of the trachea and extending up into the orifice of the right innominate artery. The aneurysm had a small sacculation, which was separated from the larger one by a fairly broad ridge, running upward in the fold of the arch. The smaller sac was $\frac{3}{4}$ inch (1.8 cm) in diameter and opened into the angle between the pericardial reflection and the anterior surface of the ascending aorta, a rupture had occurred, connecting the aneurysm directly with the pericardial cavity.

CASE 23—R G, a Negro aged 39, had apparently always been in good health. Suddenly, while in the presence of friends, on March 22, 1944, he began to gasp for air, but made no other complaints. He died in a few minutes. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were cardiac compression and syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, causing a tamponade of the heart. The valves were normal and flexible. The mouths of the coronary arteries were patent. The coronary arteries showed no lesions on section. The myocardium presented no lesions. The ascending aorta showed pearl gray plaques with longitudinal wrinkling. An aneurysm had arisen 1 inch (2.5 cm) above the aortic cusps. It was about 1½ inches (3.7 cm) in diameter and occupied the right side of the ascending aorta. In its depth it had a ¼ inch (0.6 cm) perforation, which opened directly into the pericardial cavity.

CASE 24—L D, a white man aged 65, was found lying dead in the doorway of his residence, on April 11, 1944. Cause of death was spontaneous rupture of an aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was moderately enlarged. The pericardial cavity was filled with fluid and clotted blood, which completely compressed the heart. The valves on the right side were normal. The aortic valve showed some sclerosis at the base of the cusps, there was no separation of the commissures. The mouths of the coronary arteries were patent and were not encroached on. On section the coronary arteries showed a moderate degree of sclerosis, the lumens were somewhat narrowed, although no obstruction was noted. The myocardium showed patchy distribution of fibrous streakings. The ascending aorta above the aortic valves presented the appearance of "tree bark" with pearl gray plaques intermingled with yellowish plaques, many of which were calcified. About 1 inch (2.5 cm) above the aortic valve was an aneurysm 2 inches (5 cm) in length and 1 inch (2.5 cm) in depth, this lesion had ruptured, through an opening ¼ inch (0.6 cm) in diameter, into the pericardial cavity.

CASE 25—J S, a Negro aged 36, had been ill for five days with pain in the precordial region, radiating to his back and associated with dyspnea. The attending physician had diagnosed the condition as spontaneous pneumothorax of the right side. The patient was apparently doing well when, on May 19, 1944, he went outdoors. On his return he complained of feeling bad, became extremely dyspneic and fell to the floor. He was helped to bed but died in about fifteen minutes. Cause of death was spontaneous rupture of an aneurysm of the ascending aorta, with rupture into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart weighed 700 Gm. The pericardial cavity was greatly distended with fluid and clotted blood. The valves of the heart were normal and flexible. The aortic valve cusps were thin and transparent. The commissures were not widened. The aortic ring was 7.2 cm in diameter. The ostium of the right coronary artery was slightly narrowed by the syphilitic process. The ostium of the left coronary artery was of normal caliber. On section the coronary arteries showed minimal atheromatous changes, but they were patent throughout. The myocardium was pale and flabby, but no lesions were visible on section. The entire ascending and transverse portions of the aorta, and a part of the descending aorta, showed a pronounced "pig skin" appearance of the intima, with pearly plaques. In the ascending portion of the aorta was a saccular aneurysm, with an

opening into the aorta 4.5 cm in diameter. Attached to the depth of the aneurysm was soft thrombus and on the anterior portion of this aneurysm, just below the reflection of the pericardium, a rupture 1 cm in diameter, opened directly into the pericardial cavity.

No pneumothorax was present. Both lungs contained air and showed edema and congestion.

CASE 26—J J, a white man aged 63, was suddenly taken ill, in a restaurant where he was employed, and died in a few minutes, on Sept 7, 1944. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was filled with fluid and clotted blood, compressing the heart from all sides. The valves were normal and flexible. The mouths of the coronary arteries were not encroached on, they were of normal caliber. On section the coronary arteries showed a moderate grade of sclerosis, but no obstructions. The myocardium showed only an occasional fibrous streak. There was a syphilitic process of the ascending aorta, with pearly gray plaques intermingled with yellow ones, the latter showing calcification. An aneurysm of the ascending aorta, $\frac{3}{4}$ inch (1.8 cm) in diameter, was situated at the aortic arch near its junction with the pericardial reflection. A $\frac{3}{16}$ inch (0.45 cm) perforation opened directly into the pericardial cavity.

CASE 27—O S, a white man aged 40, became ill in a hotel lobby and died in a short time, on Sept 21, 1944. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial sac. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was filled with fluid and clotted blood, which had surrounded and compressed the heart. The valves were normal and flexible. The mouths of the coronary arteries were narrowed by the syphilitic process. The coronary arteries showed no lesions on section, nor did the myocardium. The ascending aorta showed rugose, pearly white plaques, intermixed with yellowish areas of calcification. There were two small aneurysms of the ascending aorta. One, about 1 inch (2.5 cm) in diameter, was situated just above the right coronary cusp, the other, $\frac{3}{4}$ inch (1.8 cm) in diameter, was 1 inch above the posterior cusp. The wall of the latter aneurysm was very thin, a rupture in its depth, $\frac{1}{8}$ inch (0.3 cm) in diameter, opened directly into the pericardial cavity.

CASE 28—D S, a Negro girl aged 17, was about eight months pregnant, while walking on the street with her mother she collapsed and died, on Sept 24, 1945. Cause of death was spontaneous rupture of a small saccular aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy—The heart was normal in size. The pericardial cavity was completely filled with fluid and clotted blood. The valves of the heart were normal and flexible. There was no separation of the commissures. The mouths of the coronary arteries were patent and of normal caliber. The coronary arteries showed no lesions on section. The myocardium was normal. The aorta was thin walled and showed no lesions except a small aneurysm, about $\frac{3}{4}$ inch (1.8 cm) in diameter and situated over the right coronary cusp. The wall of the aneurysm showed pearl gray plaques and longitudinal wrinkling. A small vertical rupture, $\frac{1}{4}$ inch (0.6 cm), at the upper end of the aneurysm opened directly into the pericardial cavity.

CASE 29—N L, a Negro aged 50, was found lying dead on a sidewalk, on Nov 5, 1945 Cause of death was spontaneous rupture of an aneurysm of the ascending aorta into the pericardial cavity Other findings were hemopericardium and chronic syphilitic aortitis

Necropsy—The heart was normal in size The pericardial cavity was filled with fluid and clotted blood, compressing the heart The valves were normal and flexible The mouths of the coronary arteries were of normal caliber On section the coronary arteries showed a slight amount of sclerosis but no obstructions to the lumen The myocardium showed no lesions The ascending aorta showed pearly white plaques and presented a "tree bark" appearance An aneurysm, 1 inch (2.5 cm) in diameter, at the upper end of the ascending aorta, had thin walls, a soft thrombus was present in its depths A rupture about $\frac{1}{4}$ inch (0.6 cm) in diameter, located on the posterior surface of the aneurysm near the left atrium, opened directly into the pericardial cavity

SIGNIFICANT FACTORS

In all the cases reported with the exception of cases 9 and 16 an aneurysm of the ascending aorta, saccular in type, had ruptured directly into the pericardial cavity Necropsy in cases 9 and 16 showed large saccular aneurysms which were situated outside the pericardial cavity but had eroded through its lining, so that when they ruptured the opening communicated directly with the pericardial cavity, causing death by tamponade of the heart

The aneurysms reported in this series were as a rule small and had thinned-out walls Intra-aortic pressure is greatest in the ascending aorta, this factor, combined with the weakening of the wall of the aorta due to the syphilitic process, finally resulted in the blowing out of the aneurysm It is interesting to note that only in cases 21 and 27 was there more than one aneurysm A large aneurysm was present in cases 5, 6, 9, 13, 16, 20, 22 and 24, a total of 8 cases among the 29 reported in which the aneurysm was large enough to have been diagnosed ante mortem

Age—The youngest person in this series was the 17 year old Negro girl in case 28 This case was most interesting in that the small ruptured saccular aneurysm was the only evidence of syphilis at necropsy

Six persons in the series were 50 years of age or more The oldest in the series was 78 (case 5) A large massive aneurysm was found in this case, as was sclerosis of the cusps of the aortic and mitral valves, syphilis, then, was of long standing, at least ten years and perhaps longer, according to the history Large, massive aneurysms were also present in cases 6, 20 and 24, while small aneurysms were noted in cases 26 and 29 One might infer, therefore, that in the older groups the syphilitic process is also older and that therefore aneurysms are larger when they finally rupture into the pericardial cavity Sclerosis of the cusps of the aortic and mitral valves was also present in case 24

Most of the deaths were of persons in the fourth or fifth decade of life

Sex and Color—Twenty-three men and 6 women are included in this series. This bears out the observation that aneurysm is more likely to develop in men, as has been shown in other studies.

Eleven patients in this series were of the white race, 17 were Negroes and 1 was of the yellow race. This represents a higher percentage of white patients than is usual for syphilitic cardiovalvular disease.

Size of the Heart—The heart was of normal size in 20 cases, as compared with 9 in which enlargement was present. Aortic insufficiency due to separation of the commissures was noted in cases 7 and 13. Necropsy in cases 15, 18 and 25 showed normal cusps of the aortic valves and no separation of the commissures but definite dilatation of the aortic ring, due to the supravulvular syphilitic sclerosis, with resultant increase in the circumference of the aortic ring. In case 8 the enlargement was probably due to associated rheumatic valvulitis of the mitral and aortic valves. Case 24 was that of a man aged 65 with sclerosis of the mitral and aortic valves, in this case and in case 5, in which the man was 78, the process was probably due to arteriosclerosis with calcification of the aortic and mitral valves.

In cases 4 and 21 no explanation could be found for the enlargement of the heart.

Aortic Valve—The aortic valves in most cases were flexible, and there was no separation of the commissures. The exceptions have already been mentioned.

Mouths of the Coronary Arteries—In 19 cases no involvement of the mouths of the coronary arteries was recorded, in 10 cases some encroachment on both mouths was found. However, in no case had complete atresia of the mouths occurred.

COMMENT

The ascending aorta is about 5 cm. in length^{6a}. It commences at the upper part of the base of the left ventricle and passes obliquely upward, forward and to the right in the direction of the heart's axis, describing a slight curve in its course. At the union of the ascending aorta with the aortic arch, the caliber of the vessel is increased, owing to a bulging of its right wall. The ascending aorta is contained within the pericardium and is enclosed in a tube of the serous membrane common to it and the pulmonary artery. The ascending aorta is covered at its commencement by the infundibulum of the right ventricle, the trunk of the pulmonary artery and the right atrium, posteriorly, it rests on

^{6a} Gray, H. *Anatomy of the Human Body*, ed. 25, Philadelphia, Lea & Febiger, 1948.

the left atrium, the right pulmonary artery and the right bronchus. On the right side it is in juxtaposition with the superior vena cava and the right atrium, the former lying partly behind it, on the left side it is in juxtaposition with the pulmonary artery.

From the anatomic location of the ascending aorta it may be seen that aneurysms along the course of this vessel may rupture into the right atrium, the right ventricle, the conus arteriosus, the pulmonary artery, the superior vena cava, the left atrium, the right bronchus or, more commonly, directly into the pericardial cavity.

Herrmann and Schofield⁷ recently reported on the syndrome of rupture of an aneurysm of the aortic root into the right atrium. Schwab and Sanders⁸ and others⁹ reported on aortic aneurysms rupturing into the conus arteriosus of the right ventricle. Scott¹⁰ and Porter¹¹ reviewed the literature and reported on the syndrome of rupture of an aortic aneurysm into the pulmonary artery. Armstrong, Coggin and Hendrickson¹² reviewed the syndrome of rupture of an aortic aneurysm into the superior vena cava.

According to Kampmeier¹³ and to Brindley and Schwab,¹⁴ more than 50 per cent of deaths in persons with aortic aneurysm were due to rupture of the aneurysm. The usual sites of the rupture were in the left pleural cavity, the esophagus, the right pleural cavity, the vena cava, the left main bronchus and the pericardial cavity.

In the present series 27 deaths were due to rupture of the ascending aorta in that part which lies within the pericardial reflection, called the

7 Herrmann, G. R., and Schofield, N. D. The Syndrome of Rupture of Aortic Root or Sinus of Valsalva Aneurysm into the Right Atrium, *Am Heart J* **34** 87, 1947.

8 Schwab, E. H., and Sanders, C. B. Aortic Aneurysm Rupturing into the Conus Arteriosus of the Right Ventricle, *Am J M Sc* **182** 208, 1931.

9 Tompkins, R. D. Aneurysm of the Left Aortic Sinus of Valsalva with Rupture into the Right Ventricle (Intravital Diagnosis), *M Bull Vet Admin* **18** 173, 1941. Harris, W. H., Jr., and Shattenberg, A. J. Aneurysm of Aorta Rupturing into the Right Ventricle, *Ann Int Med* **20** 961, 1944.

10 Scott, R. W. Aortic Aneurysm Rupturing in the Pulmonary Artery, *J A M A* **82** 1417 (May 3) 1924.

11 Porter, W. B. The Syndrome of Rupture of an Aortic Aneurysm into the Pulmonary Artery, *Am Heart J* **23** 468, 1944.

12 Armstrong, E. L., Coggin, C. B., and Hendrickson, H. S. Spontaneous Arteriovenous Aneurysms of the Thorax. A Review of the Literature with a Report of Two Cases, *Arch Int Med* **58** 298 (Feb) 1939.

13 Kampmeier, R. H. Saccular Aneurysm of the Thoracic Aorta. A Clinical Study of Six Hundred and Thirty-Three Cases, *Ann Int Med* **12** 624, 1938.

14 Brindley, P., and Schwab, E. H. Aneurysms of the Aorta with a Summary of Pathologic Findings in One Hundred Cases of Autopsy, *Texas State J Med* **25** 757, 1930.

pericardial cavity or sac In 2 cases death was due to aneurysms which were outside the pericardial reflection but which had eroded into the pericardial cavity

Death in this condition is usually sudden, occurring in a few minutes after the rupture into the pericardial cavity Death ensues from the collection of blood in the pericardium and the tension it causes, whether by compression of the heart and the consequent prevention of diastolic expansion, or by prevention of the emptying of the cavae in the atria

Syphilitic involvement of the aortic valves and the mouths of the coronary arteries is not as a rule associated with pure saccular aneurysms of the aorta In the present series saccular aneurysms of the ascending aorta were as a rule associated with normal aortic valves, normal size of the heart and little encroachment on the mouths of the coronary arteries

If these facts are correlated, it becomes apparent that saccular aneurysms of the ascending aorta may exist without the patient's presenting any symptoms or physical signs of the disease process of the ascending aorta Only when an aortic insufficiency, atresia of the mouths of the coronary arteries or an aneurysm large enough to cause pressure symptoms or to be detected by fluoroscopic roentgenographic examination is present can the diagnosis of syphilis of the cardiovascular system be made

The fact is stressed that the possibility of small saccular aneurysms of the ascending aorta lying within the pericardial cavity should be considered in all cases in which syphilitic cardiovascular involvement is considered because of other diagnostic findings

SUMMARY

Twenty-nine cases of spontaneous rupture of a syphilitic aneurysm of the ascending aorta into the pericardial cavity, with resultant hemo-pericardium and tamponade of the heart, causing sudden death, are presented

It is difficult to diagnose this condition ante mortem because it is not as a rule associated with aortic insufficiency, enlargement of the heart or atresia of the mouths of the coronary arteries

Twenty-three men and 6 women, or 11 white persons and 17 Negroes, are included in the series

The youngest person to die was 17 years of age, the oldest, 78

Anatomically, syphilitic aneurysms of the ascending aorta may rupture into the right atrium, the right ventricle, the conus arteriosus, the pulmonary artery, the superior vena cava, the left atrium, the right bronchus or, as in this series, directly into the pericardial cavity from those portions of the ascending aorta which are not contiguous to any of the structures

DISSECTING ANEURYSMS OF THE AORTA

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REPEATED attempts have been made to ascertain the underlying etiologic factors in idiopathic cystic necrosis of the aorta since it was first described by Gsell¹ and by Erdheim². Workers have pursued several courses, among which have been the morphologic and the experimental. Among the former, the work of Erdheim is still fundamental and outstanding. He noted specifically the absence of vasa vasorum at the site of rupture in those instances in which the aorta showed the typical picture of medial necrosis. In other cases, he observed some degree of hyalinization. Despite his observations and the later work of Wiese,³ he stated the belief that the vasa vasorum did not play a role in the production of medionecrosis of the aorta. He favored the idea of some form of hyperadrenalism as the possible etiologic factor. Later workers⁴ noted alterations of the vasa vasorum.

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1 Gsell, O. Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur, *Virchows Arch f path Anat* **270** 1-36, 1928.

2 Erdheim, J. Medionecrosis aortae idiopathica, *Virchows Arch f path Anat* **273** 454-479, 1929, Medionecrosis aortae idiopathica cystica, *ibid*, **276** 187-229, 1930.

3 Weise, W. Medianekrosen, eine Untersuchung am laufenden Sektionsmaterial, *Beitr z path Anat u z allg Path* **93** 238-278, 1934.

4 (a) Moritz, A. R. Medionecrosis aortae idiopathica cystica, *Am J Path* **8** 717-734, 1932. (b) Rottino, A. Medial Degeneration of the Aorta as Seen in Twelve Cases of Dissecting Aneurysm, *Arch Path* **28** 1-10 (July) 1939, (c) Medial Degeneration in Nonruptured Aorta Appearing Syphilitic Macroscopically, *ibid* **27** 320-327 (Feb) 1939, (d) Medial Degeneration of the Aorta. Study of Two Hundred and Ten Routine Autopsy Specimens by a Serial Block Method, *ibid* **28** 337-385 (Sept) 1939. (e) Rottino, A., and Poppiti, R. Intimal Changes in Medial Degeneration of the Aorta, *ibid* **36** 201-205 (Aug) 1943.

Attempts to reproduce the lesion in rabbits by some form of injury to the vasa in the adventitia of the descending aorta or of the peripheral arteries have been made⁵ Other methods have included the injection of such drugs as epinephrine⁶ and histamine⁷ and the production of experimental shock The work of one of us (J G S),⁵ in which necrosis of the media of the aorta in dogs was produced by coagulation of the adventitia of the ascending aorta, demonstrated the importance of the nutrition of the aorta by way of the vasorum That study suggested to us that we review, with particular reference to alterations in the vasa vasorum, the histologic specimens in cases of dissecting aneurysm of the aorta

MATERIAL AND METHODS

Fourteen consecutive instances of dissecting aneurysm of the aorta, taken from the autopsy protocols of Michael Reese hospital for the years 1930 to 1947, inclusive, were reviewed from the clinical and morphologic point of view, 11 with emphasis on changes in the vasa vasorum Whenever possible, numerous blocks of tissue were examined These were taken from the relatively uninvolved zones of the aortas, as well as from the sites of rupture or perforation Sections were routinely stained with Delafield's hematoxylin and eosin and, whenever feasible, with orcein and with Masson's trichrome stain

CLINICAL FINDINGS

Age and Sex—There were 3 females and 11 males in the group, their ages ranged from 26 to 70 years, the average being 53 Three were under 40

Hypertension—In only 1 instance was there a definite history of long-standing hypertension After the onset of dissection, the systolic and diastolic blood pressures were elevated above the normal range in 4 cases The systolic pressure only was elevated in 2 additional cases and the diastolic pressure only in 2 others In the case of 1 patient, with a healed old dissection, the blood pressure was normal throughout the course in the hospital In another case, in which the patient had aortic regurgitation, the blood pressure was 140 systolic and 35 diastolic before dissection and 150 systolic and 60 diastolic after dissection Multiple small renal hemorrhages were observed in the latter instance at the postmortem examination

Onset—We obtained information about the onset of the condition in 11 cases. Pain was present in each, and it was the most conspicuous feature in all but 1 In 9, it was severe and sharp from its inception One patient had pain in the chest, slight at first, which progressively increased, the site of the pain varied,

5 Schlichter, J G Experimental Medionecrosis of the Aorta, Arch Path. 42 182-192 (Aug) 1946

6 Lange, F Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose, Virchows Arch f path Anat 248 462-604, 1924

7 Hueper, W C, and Ichniowski, C T Experimental Studies in Cardio-vascular Pathology Late Vascular Reactions of Histamine Shock in Dogs, Am. J Path 20 211-221, 1944, Hematic and Organic Reactions in Standardized and Graded Histamine Shock in Dogs, J Pharmacol & Exper Therap 78 127-138, 1943

and there was a tendency for it to shift from one area to another. The location of the pain, in most instances, could be correlated with the extent of the dissection. In 2 cases in which pain had been localized to the thorax, the dissection was found to involve most of the abdominal aorta.

Physical Findings—These data were available for 12 patients, the other 2 having died before admission to the hospital. Cardiac murmurs of assorted types, were present in 6 cases. Aortic diastolic murmurs were present in 3 cases, in 1 of which the patient had a previous old aortic insufficiency. Two patients showed physical signs of pleural effusion. In 4 cases in which the patients showed evidence of abdominal tenderness, spasm and rigidity, the dissection was found to involve the abdominal aorta. One patient⁸ had a large ecchymosis in the left lower quadrant of the abdomen, and 2 had loss of circulation in a limb.

Laboratory and Roentgenographic Findings—The white blood cell count, when available, was elevated, ranging from 10,200 to 29,900 cells per cubic millimeter. One patient, in whom the dissection involved the renal artery, had gross hematuria. Roentgenograms taken of the thorax of 3 of 5 patients showed evidence of increased aortic shadows.

Electrocardiographic Findings—Electrocardiograms were taken during the acute episode in 8 cases, with serial records in 3. In 1 instance, the record was within normal limits. Four patients showed strain of the left side of the heart, 1 patient's heart was considered abnormal, with nonspecific changes. Single records of 2 patients were considered to be indicative of possible recent myocardial infarction.

The electrocardiographic pattern of acute pericardial tamponade due to a hemopericardium was seen to develop in the case of 1 patient with strain of the left side of the heart.

It has been stated generally that the chief value of the electrocardiogram is in distinguishing dissecting aneurysm from recent myocardial infarction. However, Weiss,⁹ Wainwright¹⁰ and Baer and Goldberg¹¹ have all reported cases in which the dissection extended into the coronary artery, with resultant occlusion of the vessel and a myocardial infarction. In the present study, the electrocardiograms showed the expected evolution of recent myocardial infarctions.

Duration and Course—The duration varied. Two of our patients had old dissecting aneurysms. One of these was healed, but there was nothing suggesting its age. The other patient had had an acute episode, for which he had been hospitalized elsewhere ten months previously. At that time sudden thoracic pain developed and he lost consciousness for several hours. There was transient paralysis of the left leg and loss of pulsations in the left carotid artery and the brachial arteries, despite which the patient was able to return to work.

In the fatal cases of shortest duration, there was steady progression, usually without relief from pain, until death ensued. With 1 exception patients surviving immediate effects had gradual easing of the pain and other symptoms, but several had periodic exacerbations. After varying intervals, death occurred suddenly.

8 Green, R., and Saphir, O. Ecchymoses of the Abdominal Wall as an Early Diagnostic Sign of Dissecting Aneurysm of the Aorta, to be published.

9 Weiss, S. Dissecting Aneurysm of the Aorta. Two Cases with Unusual Features, *New England J. Med.* **218** 512-517, 1938.

10 Wainwright, C. W. Dissecting Aneurysm Producing Coronary Occlusion by Dissection of Coronary Artery, *Bull. Johns Hopkins Hosp.* **75** 81-94, 1944.

11 Baer, S., and Goldberg, H. L. The Varied Clinical Syndromes Produced by Dissecting Aneurysm, *Am. Heart J.* **35** 198-211, 1948.

Prognosis—It has been stated that about 10 per cent of dissecting aneurysms will heal¹² Two of our patients survived the initial episode, 1 dying of a recurrence and the other of congestive heart failure One of us (J G S)¹³ previously reported a case in which the patient was alive four years after the acute episode

ANATOMIC OBSERVATIONS

Heart—Hypertrophy involving primarily the left ventricle of the heart was present in almost every instance The average weight of the hearts was 565 Gm

Pronounced coronary sclerosis was present in most instances, in addition, 1 heart showed an old myocardial infarction The dissecting aneurysm had ruptured into the pericardial cavity in 6 instances

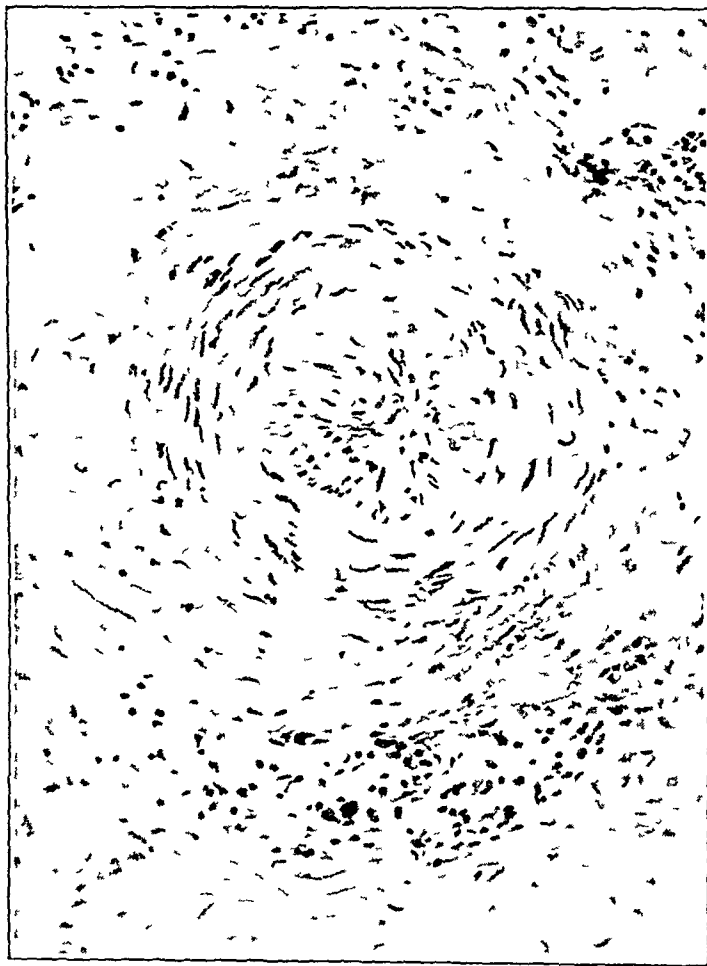


Fig 1—Small artery of the vasa vasorum, with pronounced muscular hyperplasia and intimal proliferation resulting in an extremely narrowed lumen Note small accumulations of lymphocytes in the adventitia $\times 160$, iron hematoxylin and eosin stain

Aorta—Dissecting aneurysms were present in 14 instances Medionecrosis fulfilling Erdheim and Gsell's criteria was present in 12 Two patients had extreme arteriosclerosis of the entire aorta, with many atheromatous ulcers

12 Weiss, S, Kinney, T D, and Maher, M A Dissecting Aneurysm of the Aorta with Experimental Atherosclerosis, *Am J M Sc* 200:192-203, 1940

13 Schlichter, J G Beitrag zu den Aneurysmen und Rupturen des Herzens Lausanne, Switzerland, Imprimerie Held, 1940

Dissection in these cases could be traced to undermining of the intima and the media beneath arteriosclerotic plaques, it was localized to the abdominal aorta in 1 and diffuse in the other. Alterations of the vasa vasorum were minimal in both cases, with no medionecrosis. In contrast, 2 other aortas, with moderate to pronounced atheromatosis and arteriosclerosis and with typical medionecrosis, showed profound narrowing of the vasa vasorum. Both of the latter had muscular and intimal hyperplasia of the vasa vasorum, in 1 there was also narrowing by atheromatous plaques and splitting of the intima and the internal elastic membranes of the adventitial vessels. Diffuse atheromatosis, but no arteriosclerosis, was present in another aorta with medionecrosis.

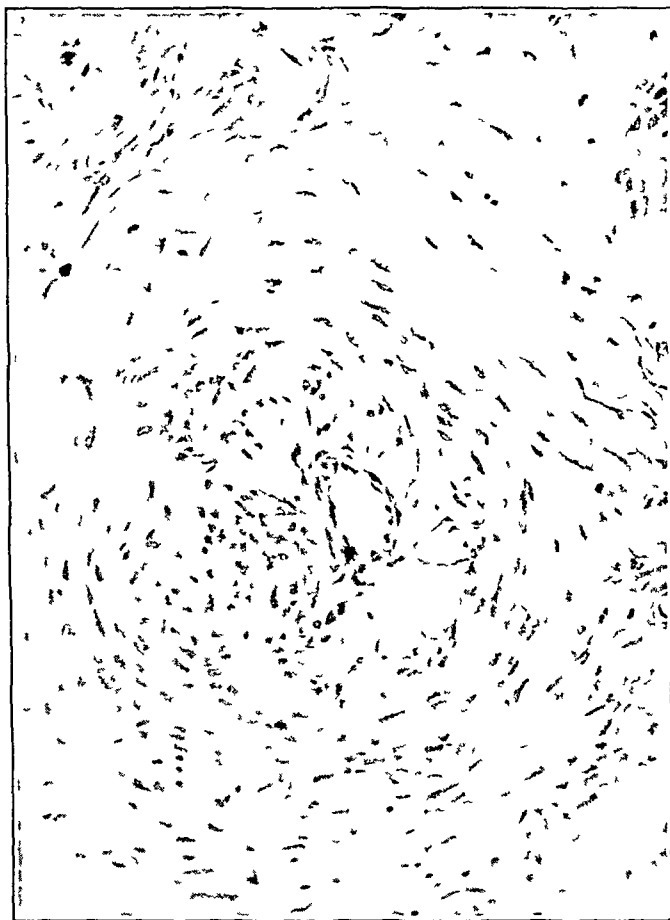


Fig 2—Small artery of the vasa vasorum, illustrating pronounced luminal narrowing resulting from subintimal deposition of lipids. $\times 160$, iron hematoxylin and eosin stain.

Two aortas with narrowings of the vasa vasorum suggested the possibility of rheumatic arteritis because of typical associated endocardial changes and because of perivascular infiltrations of the vasa vasorum.

Changes in the Vasa Vasorum—The histologic changes encountered in the cases of medionecrosis have previously been described in detail¹⁴. The vasa vasorum of 9 aortas showed narrowing of the lumens of varying types and

14 Amromin, G. D., Schlichter, J. G., and Solway, A. J. L. Medionecrosis of the Aorta, *Arch Path* 46:380-385 (Oct) 1948.



Fig 3—Roentgenogram of the vasa vasorum of the root and arch of the aorta in a patient with a dissecting aneurysm. Note lack of filling of the vasa vasorum a short distance above the cusps. This zone corresponded with the site of rupture of the dissecting aneurysm and with the most severe alterations in the vasa vasorum.



Fig 4—Roentgenogram of the vasa vasorum at the root of a normal human aorta injected with radiopaque material. The aortic cusps are at the bottom of the illustration.

severity Changes were outstanding in those aortas showing medionecrosis Alterations consisted of hyperplasia of the media (fig 1) and of splitting and reduplication of the internal elastic membrane with or without subintimal deposition of lipids (fig 2) In addition to varying combinations of these changes, the smallest vessels presented hyperplasia or swelling of endothelial cells and a collagenous type of degeneration without inflammatory reaction

The abnormalities in the vascularity of 1 aorta were demonstrated by injection of its vasa vasorum with radiopaque material, a roentgenogram of the aorta was then made (fig 3) This procedure had previously been followed by one of us (J G S) in the study of aortas removed from dogs¹⁵ as well as of normal human aortas¹⁶ (fig 4) Lack of filling of vessels near the site of rupture was seen to be associated with severe medial and intimal changes This method of demonstrating abnormalities of the vasa vasorum might well be used more frequently in instances of dissecting aneurysms and isthmus stenoses of the aorta

COMMENT

Since the original articles by Gsell and Erdheim describing medionecrosis of the aorta, there has been an increasing amount of morphologic and experimental evidence to suggest that the lesion is essentially the result of local ischemia Medionecrosis of the aorta or the peripheral vessels has been produced experimentally by chemical or mechanical interference with the vascularization, as carried out through the vasa vasorum in the adventitia⁵ Recently it was demonstrated that, through interference with the vascularization of the ascending aortas of dogs, it was possible to produce medionecrosis and its sequelae, dissecting aneurysm, spontaneous rupture or saccular aneurysm⁵

Comparing the medionecrotic lesions produced in various species of animals by a wide variety of methods with the lesion in man, one may conclude that the vascularization of the aorta determines their site, extent and severity¹⁷ Differences in the susceptibility to ischemia of the aortic wall in different species are due to variations in the vascularity of the aorta That of the rabbit is the poorest, that of the dog the richest and that of man somewhere between The excellence of the aortic vascularization of the dog may explain the difficulty encountered in attempting experimental production of medionecrosis in that animal, and the ease of experimental production of medionecrosis in the rabbit may be due to its poor vascularity¹⁷

It may be concluded, therefore, that anoxia of the vascular wall is apparently the most important factor in the development of medionecrosis Such anoxia may develop as a result of various factors

15 Schlichter, J G Studies on the Vascularization of the Aorta I The Vascularization of the Aorta in the Normal Dog, *Am Heart J* **32** 770-777, 1946

16 Schlichter, J G Vascularization of the Aorta in Different Species in Health and Disease, *Am Heart J* **35** 850-851, 1948

17 Schlichter⁵ Schlichter¹⁵

1 Obstructive or occlusive diseases of the vasa vasorum Such conditions are demonstrable morphologically, they had been noted previously in 9 of our cases There was usually arteriolosclerosis, arteriosclerosis or other alterations of the hyperplastic variety

2 Alterations in the hemodynamics of the vasa vasorum Dilatation with resultant stasis of blood may explain dissecting aneurysms first becoming manifest after shock or severe infections in man Medionecrosis experimentally produced in rabbits by injection of epinephrine (adrenalin®) may be secondary to vasoconstriction of the adventitial vessels

3 Diminished oxygen saturation of the blood or severe anemia This factor alone rarely, if ever, results in medionecrosis, however, when combined with other mechanisms it may play an important role

4 Congenital abnormalities in the distribution of the vasa vasorum or paucity of collateral circulation through the adventitia or the outer third of the media Poor vasculature may be an important cause, it can be demonstrated adequately only by injection of the vasa vasorum with radiopaque material The high frequency of dissecting aneurysm in cases of isthmic stenosis may be secondary to this factor

5 Any combination of these factors

Hypertension is important in several respects It is considered the cause of hyperplastic intimal changes of small arteries, which may include the vasa vasorum Such changes in the vasa vasorum may be the immediate or contributory cause of medionecrosis As a result of ischemia of portions of the aorta, the media undergoes infarction or necrosis The disorder may manifest itself in zones showing loss of structure or in accumulations of loose connective tissue Progression of the lesion may result in evidence of healing, as described by Erdheim² After the medionecrosis is established, even in normotensive persons, transitory hypertension, such as that produced by physical or emotional stress, may increase the spread of the dissection as well as increase its chance of rupture

The concept of zones of ischemia of the aorta has been suggested by some authors who state the belief that dissecting aneurysms may result from rupture of the vasa vasorum Such a mechanism, i e., vasospasm with necrosis of the distal portion of the vessel, could probably play a role in some cases of hypertension without histologic alterations being apparent in the vasa vasorum

The limitation or the severity of the dissection is often determined by previous pathologic changes in the aorta A vessel scarred from long-standing syphilis will rarely permit extensive spread of the dissection, presumably because of the many firm old scars Likewise, severe sclerosis of the aorta, with many large arteriosclerotic plaques

involving the intima as well as impinging on the inner portion of the media, tends to limit the spread of the dissection. A relatively normal aorta which is subjected to medionecrosis by anatomic or physiologic ischemia manifest through the vasa vasorum will usually show the most extensive dissections.

Healing of medionecrotic lesions depends to a large extent on the adequacy of collateral circulation.⁵ Even arteriosclerotic ulcers which undermine and tend to form localized or diffuse medial dissections may be limited in their spread, not only by previous scarring of the media, but also by a tendency to heal through thrombosis and scarring. The latter may be greatly facilitated when there is adequate collateral circulation through the vasa vasorum. In cases of dissection following undermining of arteriosclerotic plaques, as well as in those few cases of dissection without intimal rupture, the separation of the aortic wall from its proper blood supply may be responsible for the formation and spread of dissecting aneurysms.

The most frequent demonstrable pathologic alterations found in aortas with dissecting aneurysms are medionecrosis, undermined arteriosclerotic ulcers and, rarely, syphilitic lesions. The first is by far the commonest.

We encountered pathologic changes in the vasa vasorum in 9 of our cases of dissecting aneurysm. The changes varied from slight to pronounced arteriolosclerosis and arteriosclerosis, with hypertrophy or hyperplasia of the media and the intima. In all 9 cases, luminal narrowings were present. Abnormalities in the distribution and filling of the vascular bed were demonstrated at autopsy in the 1 aorta in which injection of the vasa vasorum with a radiopaque material was carried out.

Since some of our 14 patients were hypertensive, a recent study of the aortas of 40 patients with hypertension¹⁸ is of interest. Twenty-three of these aortas showed changes in the adventitia, with frequent accumulations of lymphocytes. In 35 per cent, however, there were hypertrophy of the media of the vasa vasorum and occasional luminal narrowing caused by subendothelial deposition of hyalin. For the most part, these findings are in accord with ours.

We examined the ascending aortas of 20 normotensive patients whose ages averaged 51.3 years. Medial hyalinization of the vasa vasorum without luminal narrowings was encountered in the cases of 5 patients, of whom 2 were 61 and 1 each 66, 72 and 76. In the aortas of 4 other patients, aged 22, 50, 66 and 73, respectively, narrowings of the lumens of the vasa vasorum were observed in addition to medial or

18 Ashworth, C. T., and Haynes, D. M. Lesions in Elastic Arteries Associated with Hypertension, *Am J Path* **24** 195-205, 1948.

intimal hyperplasia. Interestingly enough, the patient aged 22 exhibited early disruption of the outer third of the media of the aorta, resembling medionecrosis near the zones of alteration in the vasa vasorum. Luminal narrowings of a group of small arteries of the vasa vasorum in the patient aged 73 were at the immediate site of an extremely large arteriosclerotic plaque which impinged on and disrupted the inner third of the media of the aorta. Excluding these 2 persons, only 2 of the 20 routine controls had alterations of the vasa vasorum without medial or pronounced intimal changes in the aorta. These alterations were less pronounced and less extensive in comparison with those of the group with dissecting aneurysms.

Two of the dissecting aneurysms occurred in aortas with isthmic stenosis. The ages of the patients were 26 and 29, respectively. The hearts weighed 530 Gm and 400 Gm. Changes were found in the vasa vasorum of only 1 of these.

Still to be explained is the great predilection of dissecting aneurysms, particularly those which rupture, for the ascending aorta. Variability in vascularization of the ascending aorta is much greater than that of the descending aorta. Rottino¹⁴ has shown medionecrosis of the variety usually encountered in the ascending portion to be present also in the arch and in the descending aorta. How can this be reconciled with the much greater incidence of dissection at the root? Other differences are immediately evident. The ascending aorta is much more mobile and bears the greater direct brunt of the blood stream as it leaves the heart. The ascending aorta and the arch are not surrounded and protected by connective tissue and neighboring organs, as is the descending aorta. Also, the frequent ostiums arising from the aorta beyond the arch in all probability provide sufficient nourishment to the aorta directly from the lumen to compensate for any alterations or depletions in the adventitial blood supply.⁵

Reviewing our own cases and the voluminous literature on dissecting aneurysm of the aorta, it becomes apparent that this disease has not one but several backgrounds, depending on varying physiologic and morphologic alterations in the wall of the aorta. The pathologic picture itself will vary with the etiologic factor. All cases, however, have one feature in common—the destruction of the aortic media. In an aorta so damaged, normal or increased intra-aortic pressure may cause spontaneous rupture or the formation of a dissecting aneurysm and rupture.

Since destruction of the aortic media is the common feature of dissecting aneurysm, it may be suggested on the basis of evidence that the factor responsible for this idiopathic cystic necrosis of the aorta is ischemia of its media. This condition can be brought about by pathologic changes in the vasa vasorum, resulting in narrowing of their lumens. Such alterations in the vasa may be due to a localized variety

of arteriolosclerosis or arteriosclerosis and may or may not be associated with similar changes elsewhere, particularly in the kidneys

SUMMARY

The morphologic and clinical aspects of 14 cases of dissecting aneurysm of the aorta are reviewed. Two of these were due to arteriosclerosis, 12 were secondary to medionecrosis of the aorta.

Alterations were encountered in the vasa vasorum of 9 aortas, seven of the 9 showed associated medionecrosis of the aorta.

CONCLUSION

Ischemia of the media of the aorta was implicated as the underlying primary factor in the production of medionecrosis. Various experimental, physiologic, anatomic and congenital factors may, singly or in combination, bring about medionecrosis and dissecting aneurysm.

HEMATOLOGIC STUDIES IN HIROSHIMA AND A CONTROL CITY TWO YEARS AFTER THE ATOMIC BOMBING

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TABLE OF CONTENTS

Introduction

Present Day Conditions in Japan

Plan of Observation

General Data

Subjects

Precautions

General Procedures

Hematologic Procedures and Evaluation of Errors

Erythrocyte and Leukocyte Counts

Determination of Hemoglobin and Plasma Protein Content

Hematocrit Reading

Determination of Cell Constants

Differential Count

Reticulocyte Count

Laboratory Checks

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Control Studies on Americans

Statistical Procedures

Presentation of Data

Over-All Blood Picture

Relation Between Age and Sex and Response to Atomic Bombing

Relation Between Traumatic Injuries and Flash Burns and Hematologic Observations

Relation Between Amount of Radiation and Hematologic Observations

Comment

Summary

INTRODUCTION

THE ATOMIC bomb explosions in Hiroshima and Nagasaki, in August 1945, subjected large numbers of persons to significant amounts of radiation. The immediate, acute effects of the exposure have been evaluated by a group of United States Army and Navy and Japanese civilian investigators, usually referred to as the Joint Commission.¹ Their observations did much to confirm and extend the already recognized picture of acute radiation sickness and the early periods of recovery in man. There exists, then, at the present time, a considerable body of knowledge pertaining to the findings during the first few months after the exposure of man to ionizing radiation.

In contrast, relatively little is known concerning the late effects of irradiation of the whole body in man, such as may develop after apparent recovery. The data which do exist deal largely with the sequelae of repeated exposure to small doses occurring in radiologists before the necessity of adequate shielding was fully recognized, or following chronic poisoning with long-lived radioactive elements. A large number of the survivors of Hiroshima and Nagasaki, on the other hand, were persons who had received in an extremely brief time varying amounts of ionizing radiation, ranging from negligible to the maximum tolerable. The need for long range, detailed, methodical studies of the cases of these persons cannot be overstated in an era when increasing numbers of people will, in the very nature of current scientific developments, be exposed to significant amounts of radiation. Recognition of this fact resulted in the issuance, on Nov 26, 1946, of a presidential directive, charging the National Research Council with the responsibility of conducting appropriate studies of the survivors of Hiroshima and Nagasaki. The background for this directive, as well as for subsequent organizational developments, has been briefly detailed elsewhere.²

1 Report of the Joint Commission, to be published

2 Genetic Effects of the Atomic Bombs in Hiroshima and Nagasaki, Genetics Conference, Committee on Atomic Casualties, National Research Council, Science 106 331 (Oct 10) 1947

One of the foremost of the many problems clamoring for investigation relates to the cellular elements of the blood. The studies described in the present paper were carried out in Hiroshima and Kure, Japan, from March 1947 to April 1948. They were designed to answer the question: What is the peripheral hematologic picture twenty to thirty-three months after atomic bombing in persons who received large amounts of radiation to the whole body? Such studies serve the dual purpose of attempting to evaluate the current hematologic status of these persons and of providing a base line by comparison with which subsequent developments may be appreciated.

PRESENT DAY CONDITIONS IN JAPAN

A reference to health conditions in Japan at the time of this report is essential to an understanding of some of the problems and difficulties which beset a survey study of the present type. Japan suffered rather severely during the previous decade. The maintenance of a large fighting force necessarily invoked considerable privation on the general populace. Japan had never been a country of abundance and, in fact, was existing at a near equilibrium level during the prewar days. The increased demands imposed by the war reduced the general standard of living significantly beneath the initial plane. The lowest ebb of general conditions was probably reached shortly after the cessation of hostilities. During the several years previous to this report there has been a considerable improvement in living standards, but at the time of writing many essential commodities remain in short supply. Available provisions consist, for the most part, of the carbohydrate staple products, seasonal vegetables and a small amount of fish. Only on festive occasions does the average family enjoy significant amounts of animal fat and protein. The official government ration during the period covered by these studies was about 1,500 calories a day. Inflation had forced the cost of the necessary additional calories to fantastic levels.

Although a full appreciation of the true circumstances and conditions is difficult without firsthand observations, it may be appreciated that the general health conditions parallel the standard of living. This is well illustrated by the reported tuberculosis mortality rates for four years³. In 1944, there were 240.2 deaths per 100,000 persons, in 1945, 280.0, in 1946, 264.2, and in 1947, 189.0. For comparison, the mortality rate in the United States in 1945 for all forms of tuberculosis

3 Phelps, L. V., Chief, Division of Vital Statistics, Public Health and Welfare Section, General Headquarters, Supreme Commander for the Allied Powers. Personal communication to the authors.

was 40.1 deaths per 100,000 persons⁴ Imamura,⁵ in a recent photo-fluorographic survey of 144,350 persons in Osaka and its suburbs, observed 20 per cent with active tuberculosis and 15 per cent with suspected lesions. The morbidities of ascariasis and ancylostomiasis among the general population have been estimated to be from 80 to 90 per cent and from 50 to 60 per cent, respectively.⁶ Dysentery and diarrhea, due to a variety of causes, are much more prevalent than in the United States.

Thus, despite the significant accomplishments of the Public Health and Welfare Section, General Headquarters, Supreme Commander for the Allied Powers,⁷ and the strenuous postwar efforts of various Japanese groups, health conditions in Japan during the period covered by this study were significantly below those in the United States, a fact extremely pertinent to any consideration of the results described.

PLAN OF OBSERVATION

General Data—An attempt was made to compare certain aspects of the hematologic status of Japanese of Hiroshima who, at the time of the atomic bombing, had been relatively heavily irradiated with the findings for an appropriate control group. The minimum interval in man between exposure to radiation and development of such possible late hematologic complications as leukemia or aplastic anemia is known only vaguely. The rapidity and degree of completeness of hematologic recovery in a group such as that irradiated in Hiroshima is unknown. Adequate follow-up studies in Hiroshima, therefore, called for frequent sampling of the irradiated population. Unfortunately, between the termination of activities of the Joint Commission¹ and the initiation of the investigations of the Atomic Bomb Casualty Commission there elapsed, for various reasons, a period of some sixteen months, during which only a few observations were made, these were largely by

4 Natality and Mortality Data for the United States Tabulated by Place of Residence, in *Vital Statistics of the United States 1943*, United States Department of Commerce and Labor, Bureau of the Census, 1945, pt. 2.

5 Imamura, A. *The Epidemiology and Prevention of Tuberculosis in Japan*, read before the Eleventh Meeting of the Japanese Medical Association, 1947.

6 Duff, F. L. Personal communication to the authors.

7 A Review Covering a Resume of the Problems, Accomplishments, and Future Programs of the Public Health and Welfare Section Among the Japanese Population in Furthering the Objectives of the Supreme Commander, for the Period August 1945-August 1947, General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1947.

Japanese groups working under considerable handicap. Moreover, the early activities of the Atomic Bomb Casualty Commission were largely exploratory and not designed to support a large scale study. Hiroshima, in 1947, contained very little in the way of laboratory facilities, and the city was depleted of much of its native medical and technical talent. The plan whereby our observations were carried out represents a compromise between inadequate laboratory and technical facilities and the desirability of getting observations under way as quickly as possible.

Subjects—The survivors of the Hiroshima bombing received varying amounts of radiation, according to their distance from the explosion and the amount of shielding protecting them. In this first survey it was felt desirable to study those persons who had received relatively large doses of radiation. The Joint Commission had established the fact that epilation of the scalp was one of the more reliable and objective signs of the absorption of large amounts of radiation¹. It may be assumed that the majority of persons who received sufficient radiation to the scalp to cause epilation received corresponding amounts of radiation to the whole body. The epilating dose of gamma radiation of this type is estimated to be about 400 r. Consequently, epilation was utilized as the criterion for the selection of subjects. In order to control the observations on these irradiated persons, parallel studies on comparable nonirradiated persons were carried out in the city of Kure. Located 18 miles (28.97 kilometers) from Hiroshima, and about half its size, Kure is also a seaport town, with a comparable population pattern and nutritional status⁸. Being the site of a principal naval base, it had been subjected to severe incendiary and explosive bombing raids, with extensive damage, although casualties were extremely few in comparison with Hiroshima.

Precautions—Prerequisite to a study of this type are the elimination of as many undesirable varieties as possible and the observation of sufficiently large samples to validate the results statistically. Sampling was executed in such a manner as to insure maximum comparability of the two groups, aside from the factor of radiation. For instance, it was well appreciated that a large number of the survivors of Hiroshima, pretentiously suffering from "atomic bomb disease," would desire inclusion in such an investigation, with the hope of receiving treatment and advice for their ailments, the symptoms of which most conveniently dated from the atomic bombing. The inclusion of such

8 Howe, F. A. Public Health and Welfare Section, General Headquarters, Supreme Commander for the Allied Powers. Personal communication to the authors.

persons in a sample would obviously have created a bias in the form of extraneous pathologic factors, which would have been extremely difficult to duplicate in parallel controls

In order to minimize the occurrence of unrelated hematologic complications and biologic variation, as well as for reasons of convenience, it was felt desirable to study, so far as possible, the younger age groups in schools

To eliminate such systematic errors as might have arisen through the use of different groups of technicians in the two laboratories, all observations in the two cities were made by the same technicians, who alternated days between Kure and Hiroshima. During the last four months of the investigation, as many as possible of the originally selected subjects were reexamined and the results of the two observations averaged, thereby reducing seasonal changes and possible systematic laboratory errors. Actually, only about one half of the subjects were reexamined, the interval between the two examinations varying from three to eight months

Finally, to test the comparability of our technics and results with those of other investigators, a small group of 25 United States Army personnel were examined ⁹

GENERAL PROCEDURES

A random selection of epilated subjects, with the elimination of a maximum of undesirable bias of the aforementioned type, was insured through the adoption of a screening questionnaire. This included a variety of direct questions, relating to the subject's injuries and to his symptoms after the atomic bombing. The form was distributed to many of the schools in Hiroshima and likewise to a randomly selected portion of the remainder of the civil population. Approximately 16,000 screening questionnaires were completed. Those persons listing epilation were requested to report for examination. All were unaware of the criterion of selection.

In Kure, selection of the control sample was achieved through the principals of the various schools and through various local organizations, persons being selected to equate in sex and age to those actually examined in Hiroshima. All heads of organizations responsible for selection were fully appreciative of the possibility of undesirable bias arising from the inclusion of "volunteers." The accompanying histogram indicates comparison, by age and sex, of the epilated and control samples.

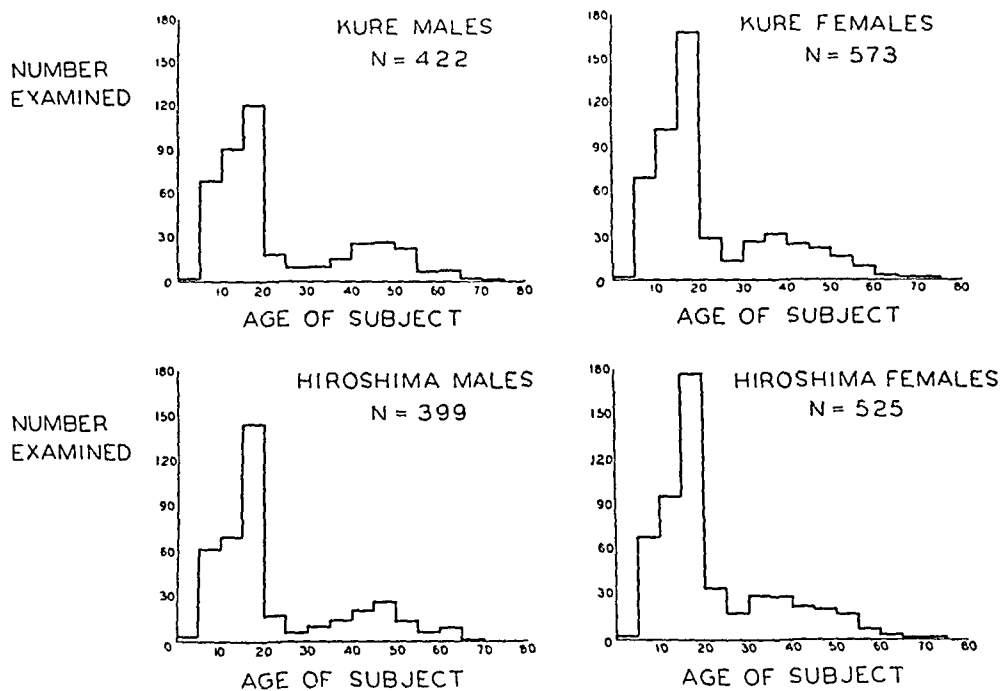
The selected subjects, on reporting to the laboratory for examination, were interviewed by a trained interpreter, who, after asking specific, direct questions, completed a detailed questionnaire. The items on the record were chosen in an attempt to bring out possible significant relations between hematologic findings and the history at the time of the bombing, with emphasis on position of the subject

9 The United States Army personnel were volunteers from the Chugoka Military Government Region and the Hiroshima Military Government Team, whose headquarters were in Kure

at the time of the explosion, signs and symptoms of radiation sickness, and associated trauma. It should not be assumed that the record in all instances represents an entirely true account, considering the fact that the interview was conducted eighteen to thirty months after an intense experience.

A similar questionnaire was used for the controls, but in the section devoted to the history only identifying information was recorded.

After the interview, a brief physical examination was carried out, with particular regard to general health, extent of injuries and occurrence of gross pathologic features. Persons with minor infections were common and were not eliminated from the series. Comparable examinations were made on both epilated and control groups. No physical examination was made at the time of reevaluation.



Frequency distribution of the population samples according to sex and age

An attempt was made to secure the following hematologic data for each subject: erythrocyte, leukocyte and differential counts, hemoglobin concentration, hematocrit reading, and plasma protein values. In addition, reticulocyte counts were obtained for a limited number of persons. Leukocyte and differential counts were made on blood flowing freely from an incision of the ear lobe. The remaining observations were made from a 5 cc sample of venous blood, drawn with no particular reference to meal time, all precautions were taken to avoid stasis. However, it should be noted that during the cold months, with the absence of adequate heating and, in some instances, adequate clothing, the peripheral circulation of the extremities was in many persons relatively static, as evidenced by slight cyanosis of the fingers. This factor introduced the possibility of some seasonal variation but did not invalidate the results, for the climatic conditions were comparable in the two laboratories. The venous sample was placed in a clean, dry tube containing 5 mg of potassium and ammonium oxalate, in the proportions

recommended by Heller and Paul¹⁰ The various hematologic determinations were usually made within an hour, and always within four hours, of the time the specimen was secured

HEMATOLOGIC PROCEDURES AND EVALUATION OF ERRORS

Erythrocyte and Leukocyte Counts—The erythrocyte count was carried out in the standard manner, using Army-Navy equipment which was not certified by the United States Bureau of Standards Dilutions of 1 200 were made with filtered Hayem's solution, samples of blood being withdrawn from the well mixed oxalated venous sample Pipets were vigorously shaken for three to five minutes just prior to filling the chamber Counting was carried out in 5 0004 cu mm volumes Duplicate dilutions and counts were made in all instances When the original pair differed by more than 400,000 cells per cubic millimeter, one or more additional dilutions and counts were made The average of all counts was taken as the final value (The practice of utilizing only that pair of a series of repeated counts on the blood of an individual subject which differs no more than a set amount is statistically an unsound procedure The establishment of a range limit, by which a pair of counts may acceptably differ, should be considered only as a means to aid in the detection of technical errors)

Leukocyte counts were also carried out in the customary manner Capillary blood was routinely employed, dilutions of 1 20 were made with filtered Turk's solution¹⁰² Pipets were vigorously shaken for three to five minutes just prior to filling the counting chamber Counting was carried out in 4 01 cu mm volumes Duplicate dilutions and counts were made in all cases When the difference between the pair of counts was greater than 20 per cent of the mean, additional dilutions and counts were made if the subject was still available, otherwise, the original pipets were reshaken and the leukocytes recounted In every case, the final value accepted was the average of all counts

The problem of error involved in the estimation of numbers of erythrocytes and leukocytes has been examined by several investigators¹¹ The work of Berkson and his collaborators^{11 e-g} was most extensive They carried out repeated dilutions and counts on a series of blood samples, utilizing standard pipets and a photographic-mechanical method of enumerating blood cells in a standard chamber

10 Heller, V G and Paul, H Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, *J Lab & Clin Med* **19** 777 (April) 1934

10a The composition of Turk's solution is described in Stitt, E R , Clough, P W , and Clough, M C Practical Bacteriology, Haematology and Animal Parasitology, ed 9, Philadelphia, P Blakiston's Son & Co, 1938, p 299

11 (a) "Student" On the Error of Counting with a Haemocytometer, *Biometrika* **5** 351 (Feb) 1907 (b) Wintrobe, M M The Size and Hemoglobin Content of the Erythrocyte Methods of Determination and Clinical Application, *J Lab & Clin Med* **17** 899 (June) 1932 (c) Ponder, E , Saslow, G , and Schweizer, M On Variations in the White-Cell Count of Man, *Quart. J Exper Physiol* **21** 21 (April) 1931 (d) Bryan, W R , Chastain, L L , and Garrey, W E Errors of Routine Analysis in the Counting of Leukocytes, *Am J Physiol* **113** 416 (Oct) 1935 (e) Magath, T B , Berkson, J , and Hurn, M The Error of Determination of the Erythrocyte Count, *Am J Clin Path* **6** 568 (Nov) 1936 (f) Berkson, J , Magath, T B , and Hurn, M Error of Estimate of Blood Cell Count as Made with Hemocytometer, *Am J Physiol* **128** 309 (Jan) 1940 (g) Berkson, J Blood Cell Count Error, in Glasser, O Medical Physics, Chicago, The Year Book Publishers, Inc, 1944, p 110

In these circumstances, the standard deviation for the determinations on any one sample was $\pm 390,000$ cells when the mean was approximately 5,000,000 cells per cubic millimeter, resulting in a coefficient of variation of $(0.390/5.00) \times 100$, or 7.8 per cent. When each item in the frequency distribution of counts was an average of duplicate dilutions and counts, the standard deviation was reduced to $\frac{1}{\sqrt{2}} \times 0.390$, or $\pm 276,000$ cells, and the coefficient of variation for the paired count means was 5.5 per cent. Approximately 95 per cent of the averages of all duplicate counts on a single blood sample might be expected to fall within $\pm 552,000$ cells (twice the standard deviation), or ± 11.0 per cent of the mean, at a mean of 5,000,000 cells.

Similarly, in regard to enumeration of leukocytes by the standard procedure, the coefficient of variation of a distribution of repeated dilutions and counts on a single sample of blood containing about 7,000 leukocytes per cubic millimeter was 10.7 per cent. The use of the averages of duplicated dilutions and counts reduced this to $\frac{1}{\sqrt{2}} \times 10.7$ per cent, or 7.6 per cent, approximately 95 per cent of paired count means might then be expected to fall within ± 15.2 per cent of the mean, if the mean were approximately 7,000 leukocytes per cubic millimeter.

The errors in these two hematologic procedures are considerably greater than is generally appreciated.

Determination of Hemoglobin and Plasma Protein Content—These determinations were made by the copper sulfate method for measuring specific gravity, as described by Phillips and others.¹² One hundred cubic centimeter portions of copper sulfate solutions, graded at intervals of 0.001 Gm per cubic centimeter, were prepared according to instructions with appropriate dilutions of a stock solution, prepared either from commercially weighed samples of copper sulfate or by the saturation technic. Each set so prepared was calibrated by direct measurement of the specific gravity of representative samples, either with a calibrated hydrometer or by comparing the weight of a filled pycnometer with that of one filled with water at the same temperature. During the last six months of the survey, the solutions were prepared in 200 cc portions and divided into two sets, one for the Kure laboratory and the other for the Hiroshima laboratory. Venous blood was used for all determinations and correction applied for the anticoagulant. Each set was used for determinations on the blood of not more than 100 persons. The bulk of the data represent single determinations, but occasionally an average of two determinations made by different independent technicians was employed. The revised nomogram was utilized to compute the hemoglobin concentration and the protein values.

The usefulness and relative accuracy of the determination of specific gravity of whole blood and plasma, in estimating the hemoglobin concentration and plasma protein content of blood, which is not grossly abnormal, have been well estab-

¹² Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Hamilton, P. B., and Archibald, R. M. *Copper Sulfate Method for Measuring Specific Gravity of Whole Blood and Plasma*, New York, Josiah Macy, Jr. Foundation, 1945.

lished,¹³ although two investigators¹⁴ have failed to demonstrate satisfactory correlation between the specific gravity of the plasma or serum and its protein content. The propriety of using this method in determinations on grossly abnormal blood is still open to question.

In an attempt to evaluate at least a portion of the error of this method in our laboratories, duplicate estimates of hemoglobin content were made by two independent technicians in 191 cases. Statistical analysis of the differences revealed no significant systematic error on the part of either technician, that is, regarding the mathematical sign of the differences, the mean difference was -0.01 ± 0.016 Gm per cubic centimeter.¹⁵ The standard deviation of the distribution of the differences was ± 0.22 Gm per cubic centimeter. Taking twice the standard deviation as indicating the significant limits of variability, 95 per cent of the absolute differences between duplicate estimations were within 0.44 Gm per hundred cubic centimeters. Utilizing the fact that the standard deviation of differences is equal to $\sqrt{2}$ times the standard deviation about the mean, one can estimate from the variation of

13 (a) Phillips and others¹² Barbour, H. G., and Hamilton, W. F. The Falling Drop Method for Determining Specific Gravity, *J Biol Chem* **69** 625 (Aug.) 1926. (b) Moore, N. S., and Van Slyke, D. D. The Relationships Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis, *J Clin Investigation* **8** 337 (April) 1930. (c) Weech, A. A., Snelling, C. E., and Goettsch, E. The Relationship Between Plasma Protein Content, Plasma Specific Gravity, and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis, *ibid* **12** 193 (Jan.) 1933. (d) Nugent, R. L., and Towle, L. W. The Specific Gravity of Synthetic Solutions of Serum Albumin and Serum Globulin, *J Biol Chem* **104** 395 (Feb.) 1934. (e) Weech, A. A., Reeves, E. B., and Goettsch, E. The Relationship Between Specific Gravity and Protein Content in Plasma, Serum, and Transudate from Dogs, *ibid* **113** 167 (Feb.) 1936. (f) Kagan, B. M. A Simple Method for the Estimation of Total Protein Content of Plasma and Serum. II The Estimation of Total Protein Content of Human Plasma and Serum by the Use of the Falling Drop Method, *J Clin Investigation* **17** 373 (July) 1938. (g) Ashworth, C. T., and Adams, G. Blood Specific Gravity Studies, *J Lab & Clin Med* **26** 1934 (Sept.) 1941. (h) Kagan, B. M. Studies on the Clinical Significance of the Serum Proteins. I The Protein Content of Normal Human Venous and Capillary Serum and Factors Affecting the Accuracy of Its Determination, *ibid* **27** 1457 (Aug.) 1942. (i) Atchley, J., Bacon, R., Curran, G., and David, K. A Clinical Evaluation of the Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, *ibid* **30** 830 (Oct.) 1945. (j) Hynes, M., and Lehmann, H. The Accuracy of Haemoglobin Determination by the Copper Sulfate-Blood Gravity Method in Indian Soldiers, *J Physiol* **104** 305 (Jan.) 1946. (k) Meyer, F. L., Abbott, W. F., Allison, M., and McKay, C. Comparison of Plasma Protein Concentration, Hemoglobin and Hematocrit Values Determined by Chemical Methods and Calculated from Specific Gravity, *Arch Biochem* **12** 359 (March) 1947.

14 (a) Zozaya, J. A Physicochemical Study of Blood Sera, *J Biol Chem* **110** 599 (Aug.) 1935. (b) Looney, J. M. The Relation Between Specific Gravity of Blood Serum and Its Protein Concentration, *J Lab & Clin Med* **27** 1463 (Aug.) 1942.

15 All errors given in this paper are standard errors.

differences between two determinations of hemoglobin content, the variation about a mean value for hemoglobin content. Thus, the standard deviation about the mean

equals $\frac{\pm 0.22}{\sqrt{2}}$, or ± 0.156 Gm, and 95 per cent of the values might be expected

to fall within twice the standard deviation (± 0.31 Gm) or, at an assumed mean of 13 Gm per hundred cubic centimeters, within ± 2.4 per cent of the mean. The last value, then, is an estimate at a fiducial limit of 0.95 of the error in determination of hemoglobin concentration by the method of observed differences in specific gravity.

Similar treatment of the differences in 191 duplicate estimations of plasma protein contents gave a mean difference of $+0.003 \pm 0.015$ Gm per hundred cubic centimeters when the mathematical sign of the differences was taken into consideration. The standard deviation was ± 0.20 Gm, again, if twice the standard deviation were taken as indicating the significant limits of variability, 95 per cent of the differences might be expected to fall within 0.40 Gm per hundred cubic centimeters. Again, the 95 per cent expected variation about a

mean plasma protein value was $\frac{\pm 0.40}{\sqrt{2}} = \pm 0.28$ Gm, or within ± 3.7 per cent

of a mean of 7.5 Gm per hundred cubic centimeters. When one again assumes a fiducial limit of 0.95, ± 3.7 per cent is an estimate of the error in determination of plasma protein content by the method of observed differences in specific gravity.

Hematocrit Reading—All hematocrit readings were made with Wintrobe tubes,¹⁶ utilizing oxalated venous blood. The tubes were centrifuged routinely for one hour at 3,300 revolutions per minute in a centrifuge with a radius of 15 cm from the midpoint of the hematocrit tube, or at 4,000 revolutions per minute in a centrifuge with a radius of 10 cm from the midpoint of the tube. This resulted in equal centrifugal force in the two centrifuges.¹⁷ The buffy coat layer was not included in the reading. In an attempt to evaluate the personal error involved in reading the hematocrit, duplicate readings were made by two independent technicians in 192 cases. Statistical analysis of the results, taking the mathematical sign of the differences into consideration, revealed that there was a slight systematic variation between the work of the two technicians. The mean difference was -0.082 ± 0.017 cc per hundred cubic centimeters, a systemic error of only 0.18 per cent at a mean of 45.0 cc per hundred cubic centimeters. The standard deviation of the frequency distribution of the differences was ± 0.24 per cent, and 95 per cent of the absolute differences might be expected to be within 0.48 per cent. The 95 per cent level of variability about

a mean is given by the calculation $2 \times \frac{0.24}{\sqrt{2}}$, or ± 0.34 per cent, this variability

being due to the error involved in the reading of a hematocrit. Therefore, at a mean of 45 per cent and a fiducial limit of 0.95, this error is estimated at 0.76 per cent. Moreover, the error has been shown to be systematic, on the average, one technician read slightly, but significantly, higher than the other.

In the attempt to evaluate the error in the hematocrit readings due to differences in tubes and to the personal error introduced by a single observer,

16 Wintrobe, M. M. *Clinical Hematology*, ed. 25, Philadelphia, Lea & Febiger, 1946.

17 International Centrifuge Catalogue, 1944.

fifty-two determinations were made on the same blood, utilizing fifty-two different tubes, all of which were read by the same person. The mean hematocrit reading in this experiment was 47.84 per cent, with a standard deviation of ± 0.27 per cent. This indicates that 95 per cent of observations might be expected to fall within ± 0.54 per cent (twice the standard deviation), or ± 1.13 per cent of the mean.

The variance due to the error involved in reading a hematocrit has been estimated at $\overline{0.17}^2$, or 0.0289, per cent. The variance due to this source of error plus the error introduced by the use of different tubes has been estimated at $\overline{0.27}^2$, or 0.0729, per cent. The difference between these two variances, or 0.0440 per cent, is a rough estimate of the variance introduced by differences in hematocrit tubes. The latter source of error, therefore, appears to outweigh the personal error.

Determination of Cell Constants—The cell constants, mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration, were routinely calculated in the usual manner.¹⁸ A preliminary discussion of the error involved in the determination of these ratios and of the variability of normal values seems indicated at this point.

The normal mean cell volume for healthy adults is commonly stated to be 87 cubic microns and the normal range from 82 to 92 cubic microns.¹⁹ The mean has been confirmed, but the basis on which the normally accepted range rests is probably less secure. Pearson,²⁰ in 1897, reported an equation for the standard deviation of a ratio of two variables where the coefficient of variation of the numerator and denominator and the degree of correlation between them are known.

$$SD_{\frac{y}{x}} = \frac{\bar{y}}{\bar{x}} \sqrt{v_x^2 + v_y^2 - 2r_{xy}v_xv_y},$$

in which $SD_{\frac{y}{x}}$ is the standard deviation of the ratio $\frac{y}{x}$, \bar{x} is the mean of the first variable, \bar{y} is the mean of the second variable, y , v_x and v_y are the coefficients of variation of the two variables, x and y , expressed as simple proportions rather than as percentages, and r_{xy} is the coefficient of correlation of x and y .

One may assume, for the moment, that one is dealing with a single sample of blood and that repeated erythrocyte counts and hematocrit determinations have been made. In this instance r is zero, since separate subsamples are used for the determinations. The coefficients of variation due to error inherent in the procedures have been estimated in the foregoing paragraphs. Applying

18 Wintrobe, M. M. (a) ^{11b}, (b) ¹⁶, (c) Direct Calculation of the Volume and Hemoglobin Content of the Erythrocyte, *Am J Clin Path* **1** 147 (March) 1931.

19 Wintrobe, M. M. (a) ¹⁶, (b) ^{18c}, (c) Wintrobe, M. M. Blood of Normal Men and Women, *Bull Johns Hopkins Hosp* **53**:118 (Sept) 1933, *Anemia*, *Arch Int Med* **54** 256 (Aug) 1934.

20 Pearson. On a Form of Spurious Correlation Which May Arise when Indices Are Used in the Measurement of Organs, *Proc Roy Soc London* **60** 489, 1897.

these data to the preceding equation, the expected variation in the mean cell volume can be calculated. Assuming a single estimate of the erythrocyte count ($v_x = 0.078$), a single hematocrit determination ($v_y = 0.0057$), and single values for the mean ($\bar{x} = 5,000,000$ cells per cubic millimeter and $\bar{y} = 43.5$ per cent) the computation is

$$\begin{aligned} S D_{\frac{y}{\bar{x}}} &= \frac{43.5}{500} \times 10 \sqrt{(0.078)^2 + (0.0057)^2} \\ &= 87 \sqrt{61.16 \times 10^{-4}} \\ &= \pm 87 (7.82 \times 10^{-2}) \\ &= \pm 6.8 \text{ cubic microns}^{21} \end{aligned}$$

This value signifies that in a single sample of blood, with means as just assumed, 95 per cent of the determined values for mean cell volume may be expected to fall within a range of twice the standard deviation, or 73.4 to 100.6 cubic microns. The utilization of the average of duplicate erythrocyte counts and hematocrit determinations in the calculation of the values for mean cell

volume would reduce the variation to $\frac{S D_{\frac{y}{\bar{x}}}}{\sqrt{2}}$, or ± 4.8 cubic microns and

thereby reduce the range for 95 per cent of the values to 77.4 to 96.6 cubic microns.

The utilization of the average of additional determinations in a similar manner

would reduce the error further, in the proportion of $\frac{1}{\sqrt{n}}$, in which n is the number

of determinations averaged.

One may now consider a population of normal men, for whom the mean erythrocyte count is 5,500,000 cells per cubic millimeter, the mean hematocrit reading is 47.8 per cent and the respective standard deviations, based on duplicate determinations, are $\pm 380,000$ cells and ± 3.0 per cent. (These standard deviations are only an estimate and serve here simply as an illustrative assumption. The literature shows considerable variation from investigator to investigator.²² Simi-

21 The constant 10 is introduced in order that the result may be expressed in cubic microns.

22 (a) Ashworth and Adams^{18g} (b) Wintrobe^{19c} (c) Wintrobe, M. M., and Miller, M. W. Normal Blood Determinations in the South, Arch Int Med. 43:96 (Jan) 1929. (d) Wintrobe, M. M. Blood of Normal Young Women Residing in a Subtropical Climate, ibid 45:287 (Feb) 1930. (e) Foster, P. C., and Johnson, J. R. Oxygen Capacity and Hemoglobin Content of Normal Blood of Men, Proc Soc Exper Biol & Med 28:929 (June) 1931. (f) Walters, O. S. Normal Erythrocyte, Hemoglobin, and Packed Cell Volume Standards in Young Men, J Lab & Clin Med 19:851 (May) 1934. (g) Linneberg, L. L., and Schartum-Hansen, H. Hemoglobin Content of Blood and Number and Volume of Red Blood Corpuscles in Healthy Men and Women, Norsk mag f lægevidensk. 96:832 (Aug) 1935. (h) Price-Jones, C., Vaughn, J. M., and Goddard, H. M. Hematological Standards of Healthy Persons, J Path & Bact 40:503 (May) 1935. (i) Osgood, E. E. Normal Hematological Standards, Arch Int Med 56:849 (Nov) 1935. (j) Belk, P., Curtis, E., and Wilson, M. Erythrocyte Counts, Hemoglobin and Erythrocyte Volume in Normal Young Men and Women

larly, the variability of hemoglobin concentration in a sample of healthy men may be estimated as ± 0.90 Gm, at a mean of approximately 16 Gm per hundred cubic centimeters. This standard deviation for the erythrocyte count of a population is only slightly greater than Berkson's standard deviation for repeated duplicate determinations on the same sample. The discrepancy between theory and "observation" may well be a result of the sampling bias introduced by the probably not infrequent statistical malpractice of repeating, because of too rigid criteria of acceptability, those counts which look "off" and then accepting only those which appear more "reasonable," discarding the "off" counts as errors in technic, when actually they may well be chance variations.) These values would have corresponding coefficients of variation of 6.91 and 6.28 per cent. One may assume that the correlation coefficient between these two determinations is 0.60 (The correlation coefficient, as calculated from data appearing in the literature,²¹ likewise shows considerable variation, ranging from 0.10 to 0.75. The value quoted previously is a working estimate. In the present study, the correlation coefficients for 143 male control subjects aged 15 to 30 were 0.529 for erythrocyte count and hematocrit reading, 0.569 for hemoglobin concentration and erythrocyte count, and 0.782 for hematocrit reading and hemoglobin concentration. On substitution of the aforementioned assumed values in the equation, the standard deviation of the mean cell volume is estimated to be ± 5.2 cubic microns. The mean plus or minus twice this value indicates an estimate of the range within which 95 per cent of the values of mean cell volume for the assumed population might be expected to fall. The range would be 76.6 to 97.4 cubic microns. In this instance, the utilization of additional erythrocyte counts and hematocrit readings, to calculate the mean cell volume for each person, would not reduce the variation by

$\frac{1}{\sqrt{n}}$, but by somewhat less, for in following such a procedure one can only

approach the true biologic variation.

In a similar manner, assuming approximate coefficients of variation of the hematologic determinations, as mentioned previously, one can calculate the expected ranges of the other cell constants, mean cell hemoglobin and mean cell hemoglobin concentration. For determinations on a single blood sample, then, the means and

Residing in the Eastern United States, *Am J Clin Path* **6** 487 (Sept.) 1936 (h) Hamre, C. J., and Wong, K. K. L. Hematologic Values for Normal Children Three, Four and Five Years of Age Living in Hawaii, *Am J Dis Child* **60** 22 (July) 1940. (i) Hamre, C. J., and Wong, K. A Survey of Hemoglobin and Blood Cell Levels of Pre-School Children, Special Publication 34, Hawaii Academy of Science, 1940. (m) Hamre, C. J., and Au, M. H. Hematologic Values for Normal Healthy Men Sixteen to Twenty-Five Years of Age, *J Lab & Clin Med* **27** 1231 (July) 1942. (n) Heath, C. W. The Hemoglobin of Healthy College Under-Graduates and Comparisons with Various Medical, Social, Physiologic and Other Factors, *Blood* **3** 566 (May) 1948. (o) Valentine, W. N., and Neel, J. V. A Statistical Study of the Variables in Subjects with Thalassemia Minor, *Am J M Sc*, to be published. (p) Price-Jones, C. The Concentration of Hemoglobin in Normal Human Blood, *J Path & Bact* **34** 779 (Nov.) 1931. (q) Myers, V. C., and Eddy, H. M. The Hemoglobin Content of Human Blood, *J Lab & Clin Med* **24** 502 (Feb.) 1939.

23 Wintrobe and Miller^{22c} Foster and Johnson^{22e} Walters^{22f} Linneberg and Schartum-Hansen^{22g} Belk, Curtis and Wilson^{22j}

standard deviations are 290 ± 23 micromicrograms for mean cell hemoglobin and 34 ± 0.45 per cent for mean cell hemoglobin concentration, utilizing single hematologic determinations in computation of the ratios. The standard deviations would be

reduced by $\frac{1}{\sqrt{2}}$ if the average of duplicate determinations were employed in the computation.

One may assume that in the case of a population sample, the correlation coefficient between erythrocyte count and hemoglobin concentration and between hemoglobin concentration and hematocrit reading is 0.60, and that standard deviations for the population are as previously mentioned (erythrocyte count, $\pm 380,000$ cells, hemoglobin concentration, ± 0.90 Gm, and hematocrit reading, ± 3.0 per cent), thus giving, at their respective means, coefficients of variation of 6.91 per cent, 5.62 per cent and 6.28 per cent. In a normal population, then, the ranges of variability of 95 per cent of values about the means of the mean cell hemoglobin and mean cell hemoglobin concentration become 290 ± 3.4 micromicrograms and 34 ± 3.6 per cent, respectively.

By utilizing the averages of repeated determinations for each person, one can only approach the true biologic variation.

Differential Count—Blood films were prepared from free-flowing capillary blood by the cover slip technic. The prepared films were routinely stained with Wright's stain. The differential counts were made only by physicians. Two hundred or more consecutive cells were differentiated. All films were checked by one of us (J. V. N. or F. M. S.), and in cases of apparent discrepancies, additional cells were differentiated and averaged with the previous differential count.

The question of the error involved in the differential count, expressed as a percentage, received adequate treatment by Goldner and Mann²⁴. They stated the belief that the greatest error was the statistical error of sampling and that the variability could, in spite of skewness of distribution in case of means on either side of 50.0 per cent, be estimated with reasonable accuracy by the formula for

the standard deviation of a percentage. The formula is $SD = \sqrt{\frac{pq}{n}}$, where n

is the number of cells counted, p is the estimate of the mean percentage of the cell in question and q is $100 - p$. Thus, at a mean neutrophil count of 60 per cent,

based on the differentiation of 200 cells, $SD = \sqrt{\frac{60 \times 40}{200}} = \pm 3.46$ per cent, and

95 per cent of successive differential counts on 200 cells of this blood might be expected to fall within ± 6.9 per cent of the mean of 60 per cent. Ponder and others²⁵ stated that a considerable portion of the error in differential counts depended on the technics of preparation.

Reticulocyte Count—Reticulocytes were stained vitally by the method described by Osgood and Wilhelm²⁵. Smears were then prepared in the usual manner and counterstained with Wright's stain. The number of reticulocytes per 3,000 erythrocytes was counted in each case and the percentage computed.

24 Goldner, F. M., and Mann, W. M. The Statistical Error of the Differential White Count, *Guy's Hosp. Rep.* 88:54 (Jan.) 1938.

25 Osgood, E. E., and Wilhelm, M. M. Reticulocytes, *J. Lab. & Clin. Med.* 19:1129 (July) 1934.

The variation involved in the estimates of reticulocytes on a percentage basis (not in absolute number, since this would likewise involve the error of estimation in the erythrocyte count) may probably be assumed to follow the gaussian curve of error in a manner similar to that of the error in the differential counts. If such is the case, limits of variability for 95 per cent of values may be estimated at

$$2 \sqrt{\frac{1 \times 99}{3,000}}, \text{ or } \pm 0.36 \text{ per cent, at a mean of 1 per cent and with the count based}$$

on a total of 3,000 cells

Laboratory Checks—Further to insure the reliability of our hematologic procedures, from time to time during the course of the study a 10 cc sample of venous blood was drawn from a subject, unknown to the staff of technicians. The sample was divided into two of the usual 5 cc portions and treated in the laboratory as

TABLE 1—*Mean Hematologic Values and Standard Deviations in United States Army Personnel*

Observation *	Number of Subjects	Mean and Standard Error	Standard Deviation
Erythrocyte count	25	5,674,000 \pm 114,000	\pm 570,000
Hemoglobin concentration	25	15.97 \pm 0.19	\pm 0.93
Hematocrit reading	25	47.94 \pm 0.50	\pm 2.50
Mean cell volume	25	89.9 \pm 1.4	\pm 7.0
Mean cell hemoglobin	25	29.5 \pm 0.4	\pm 2.0
Mean cell hemoglobin concentration	25	33.4 \pm 0.3	\pm 1.4
Leukocyte count	24	8,034 \pm 481	\pm 2,359
Neutrophils	18	60.6 \pm 1.8	\pm 7.7
Lymphocytes	18	30.3 \pm 1.5	\pm 6.5
Monocytes	18	6.0 \pm 0.6	\pm 2.6
Eosinophils	18	2.8 \pm 0.4	\pm 1.9
Plasma protein value	25	7.66 \pm 0.05	\pm 0.38

* In this and subsequent tables, erythrocyte count is expressed in cells per cubic millimeter; hemoglobin concentration, in grams per hundred cubic centimeters; hematocrit reading, in per cent; mean cell volume, in cubic microns; mean cell hemoglobin, in micromicrograms; mean cell hemoglobin concentration, in per cent; leukocyte count, in cells per cubic millimeter; differential count values, in per cent; and plasma protein values, in grams per hundred cubic centimeters.

the blood of 2 individual subjects. Analysis of the differences in fifteen such tests indicated variations within the limits of error of the technics.

CONTROL STUDIES ON AMERICANS

The mean values and respective standard deviations for the various hematologic procedures performed on 25 United States Army volunteers are presented in table 1. The subjects formed a group of healthy young men who had a rather heterogeneous racial background. For instance, the series included second generation Japanese and Chinese. Hamre and others^{22k-m} found no significant racial differences in the cellular elements of the blood in persons in the Hawaiian islands, having studied the problem rather extensively in a variety of age groups.

It may be noted in table 1 that the mean values for the various hematologic determinations agree with the usually accepted means.^{14a} The variabilities about the means, however, are somewhat higher than the usual standards. This question of acceptable variability has been discussed and will be returned to again near the end of this report.

TABLE 2—Over-All Comparison of Hematologic Differences Between Subjects in Hiroshima and Those in Kure

Observation	Subjects in Kure			Subjects in Hiroshima			Value for F Test §	No of Pairs	Mean Difference and Standard Error \pm
	No of Ob serva tions	Mean and Standard Error	Standard Deviation	No of Ob serva tions	Mean and Standard Error	Standard Deviation			
Erythrocyte count	709	4,604,000 $\pm 17,000$	$\pm 442,000$	629	4,521,000 $\pm 20,000$	$\pm 501,000$	3.2	129	437 $\pm 65,000$ $\pm 27,000$
Hemoglobin concentration	912	13.14 ± 0.041	± 1.25	872	12.84 ± 0.040	± 1.31	4.9	115	447 ± 0.30 ± 0.081
Hematocrit reading	802	41.46 ± 0.13	± 3.60	757	40.98 ± 0.14	± 3.73	2.5	108	± 0.48 ± 0.19
Mean cell volume	629	87.85 ± 0.28	± 6.90	546	88.34 ± 0.30	± 7.26	1.2	111	± 0.49 ± 0.41
Mean cell hemoglobin	708	28.74 ± 0.088	± 2.34	627	28.55 ± 0.14	± 2.59	1.2	123	433 ± 0.19 ± 0.16
Mean cell hemoglobin concentration	665	32.15 ± 0.053	± 1.37	757	32.20 ± 0.052	± 1.43	0.7	109	± 0.05 ± 0.074
Plasma protein value	912	7.59 ± 0.017	± 0.500	872	7.65 ± 0.019	± 0.549	2.4	121	443 ± 0.08 ± 0.025
Leukocyte count	707	9,908 ± 101	$\pm 2,693$	645	9,847 ± 122	$\pm 3,100$	0.4	132	455 ± 56 ± 160
Neutrophils	707	54.96 ± 0.35	± 9.35	637	54.96 ± 0.39	± 9.94	0.0	113	432 ± 0.00 ± 0.53
Lymphocytes	707	29.40 ± 0.28	± 7.54	637	28.01 ± 0.31	± 7.89	3.5	110	432 ± 1.39 ± 0.42
Monocytes	707	6.36 ± 0.085	± 2.26	637	6.33 ± 0.093	± 2.35	0.2	108	432 ± 0.03 ± 0.13
Eosinophils	707	8.93 ± 0.26	± 7.02	637	10.76 ± 0.32	± 7.97	4.5	129	432 ± 1.83 ± 0.41
Reticulocyte count *	133	0.89 ± 0.03	± 0.38	120	0.96 ± 0.04	± 0.49	1.4	172	± 0.07 ± 0.05

* In this and subsequent tables, reticulocyte count is expressed in per cent of erythrocytes

† In this and subsequent tables, differences carrying a plus sign indicate a higher value for control subjects and those carrying a minus sign, a higher value for epilated subjects

‡ Values for t in excess of 2.0 indicate differences significant at the probability level of 95 per cent, values in excess of 2.6 differences significant at the 99 per cent probability level

§ Values for F in excess of 1.16 indicate differences significant at the probability level of 95 per cent, values in excess of 1.24, differences significant at the 99 per cent probability level

¶ In this and subsequent tables, differences greater than twice their errors are indicated with bold face type

STATISTICAL PROCEDURES

Although every effort was made to establish two subpopulations within the cities of Kure and Hiroshima comparable in all respects except exposure to an atomic bombing, there existed within each of these two populations considerable hematologic variability, introduced by such well recognized factors as age and sex. Comparison of the two populations in terms of the means and the standard error of the difference is a relatively crude statistical procedure, since in these circumstances the standard error of the means, on which the evaluation of the significance of any observed difference rests, receives a substantial contribution of variation from the aforementioned factors, which are of no particular interest in the present study. In order to refine the comparison of the two groups, each epilated person was paired at random with a control subject of the same sex and of similar age. The differences between the corresponding hematologic values of these pairs were then treated statistically. Once pairs had been established, the same pairs were retained for all subsequent analysis. Since only those persons who had been seen twice were included in this paired series, the total number of pairs which could be established was far less than the number of observations, so that this procedure, while inherently more sensitive, entailed sacrificing a considerable number of observations. However, the procedure did avoid, in part, the necessity of establishing multiple regression equations for adequate comparison of the two groups. It was felt that the survey was not sufficiently complete, in many respects, to justify treatment of the data by the more elaborate analysis of covariance.

PRESENTATION OF DATA

Over-All Blood Picture—Table 2 presents the mean, standard deviation, and standard error of the mean for all the hematologic determinations carried out in Hiroshima and Kure, as well as a summary of the gross differences between subjects in the two cities. These differences are expressed in two ways, first as the differences between the means of the various determinations carried out in the two cities, and secondly as the mean differences between the series of the aforementioned paired individual subjects. In both methods, the *t* statistic was used to evaluate the significance of any observed difference. With samples of this size, any value of *t* in excess of 20 indicates a difference significant at the 95 per cent probability level, whereas a value in excess of 26 denotes a difference significant at the 99 per cent probability level. Differences greater than twice their errors, corresponding to a *t* value in excess of 20, are printed in bold face type in all tables. Differences are listed with an arithmetical sign, + indicating a higher value for controls, and — indicating a higher value for epilated persons.

Because most of the hematocrit determinations were made during the latter part of the study, there were not sufficient duplicate observations on the same persons to warrant an analysis by differences of the established pairs, a fact which resulted in the omission also of the analysis of mean cell volume and mean cell hemoglobin concentration by this method. The small number of reticulocyte counts likewise did not justify an analysis of the differences of established pairs. These omissions are also evident in subsequent tables.

A number of interesting facts emerge from a study of table 2.

1 Determinations of erythrocyte count and hemoglobin concentration, by both types of analysis, were slightly lower in Hiroshima than in Kure. Hematocrit

values were also lower in Hiroshima. These differences are of statistical significance. There is, on the other hand, no significant difference with respect to differences in mean cell volume, mean cell hemoglobin or mean cell hemoglobin concentration. The differences between the two series, epilated subjects and control subjects, thus appear to be quantitative rather than qualitative. However, a discussion of standard deviations appears later in this report.

2 Leukocyte levels were practically identical in the two cities and were probably on the high side by American standards. However, there appeared to be slight differences in the percentage values for some of the various types of leukocytes. By comparison with Kure, the number of lymphocytes showed an absolute depression of 1.39 per cent in Hiroshima, and the number of eosinophils was elevated by 1.83 per cent. These differences, although small, are statistically significant.

3 Plasma protein values were slightly higher in Hiroshima than in Kure but the significance of the difference is problematic. In both cities, plasma protein values were slightly elevated by American standards.

4 For every hematologic characteristic studied, the standard deviation was larger in Hiroshima than in Kure. Taken singly, these differences are not striking. However, because of the large numbers involved, they are, in several cases, statistically significant, as indicated by the F test, on which data are included in table 2.²⁶ With the number of degrees of freedom involved here, a value of F in excess of 1.16 indicates a difference significant at the 95 per cent probability level and one in excess of 1.24 exceeds a 99 per cent probability level. Six of the thirteen values exceed the 95 per cent level and four of these, the 99 per cent level. Moreover, the facts that the differences are, in all instances, in the same direction and that the value for F , in all instances, exceeds 1.08 are of themselves of great significance. It may be concluded that the Hiroshima population studied was hematologically more variable than that studied in Kure.

There were, then, a number of slight, yet statistically significant, differences between the peripheral hematologic pictures in the two cities. The appreciation of the meaning of these differences can perhaps be furthered through additional analysis of the data with respect to these questions:

1 Is there evidence that any particular age or sex group contributed disproportionately to the observed differences?

2 Is there evidence that the traumatic injuries and flash burns which were so frequent and severe in Hiroshima played a role in the hematologic difference?

3 Is there evidence that the amount of radiation over and beyond the minimal epilating dose, as estimated by distance from the hypocenter of the explosion, extent of epilation or degree of severity of radiation sickness, influenced the final picture?

Relation Between Age and Sex and Response to Atomic Bombing—A breakdown of the results of hematologic observations on the control and epilated groups, with respect to age and sex, is given in tables 3 and 4. Data are not distinguished with respect to sex at ages below 14. Although the control figures on normal Japanese subjects bring out the number of facts of general hematologic interest,

26 Snedecor, G. W. *Statistical Methods Applied to Experiments in Agriculture and Biology*, ed. 4, Ames, Iowa, Iowa State College Press, 1946.

TABLE 3—*Relation Between Age and Sex and Hematologic Findings*

Observation	Age, Years *	Subjects in Kure					
		Male			Female		
		Number	Mean and Standard Error	Standard Deviation	Number	Mean and Standard Error	Standard Deviation
Erythrocyte count	0-9	99	4,714,000 \pm 38,000	\pm 0 378			
	10-14	111	4,646,000 \pm 32,000	\pm 0 340			
	15-19	101	4,882,000 \pm 37,000	\pm 0 368	84	4,633,000 \pm 52,000	\pm 363,000
	20-39	52	4,804,000 \pm 53,000	\pm 0 383	95	4,386,000 \pm 48,000	\pm 466,000
	40 and above	90	4,562,000 \pm 48,000	\pm 0 457	77	4,188,000 \pm 42,000	\pm 372,000
Hemoglobin concentration	0-9	136	12 65 \pm 0 050	\pm 0 93			
	10-14	187	12 86 \pm 0 063	\pm 0 86			
	15-19	118	14 19 \pm 0 105	\pm 1 14	157	12 96 \pm 0 080	\pm 1 00
	20-39	51	14 45 \pm 0 122	\pm 0 87	96	12 59 \pm 0 126	\pm 1 24
	40 and above	90	13 94 \pm 0 140	\pm 1 33	77	12 26 \pm 0 132	\pm 1 16
Hematocrit reading	0-9	119	39 11 \pm 0 22	\pm 2 41			
	10-14	171	39 93 \pm 0 15	\pm 2 00			
	15-19	116	44 05 \pm 0 32	\pm 3 40	137	40 93 \pm 0 23	\pm 2 74
	20-39	44	46 14 \pm 0 45	\pm 2 96	77	40 67 \pm 0 40	\pm 3 55
	40 and above	74	45 08 \pm 0 43	\pm 3 69	64	39 88 \pm 0 43	\pm 3 47
Mean cell volume	0-9	95	83 23 \pm 0 55	\pm 5 35			
	10-14	109	85 06 \pm 0 55	\pm 5 76			
	15-19	99	88 15 \pm 0 64	\pm 6 34	67	86 88 \pm 0 76	\pm 6 19
	20-39	44	91 00 \pm 0 89	\pm 5 88	77	89 08 \pm 0 80	\pm 7 06
	40 and above	74	93 22 \pm 0 82	\pm 7 09	64	90 13 \pm 0 75	\pm 6 04
Mean cell hemoglobin	0-9	99	26 85 \pm 0 18	\pm 1 76			
	10-14	111	27 68 \pm 0 18	\pm 1 91			
	15-19	101	29 25 \pm 0 19	\pm 1 89	84	28 24 \pm 0 22	\pm 1 97
	20-39	51	30 17 \pm 0 27	\pm 1 94	95	28 75 \pm 0 25	\pm 2 40
	40 and above	90	30 67 \pm 0 22	\pm 2 12	77	29 36 \pm 0 25	\pm 2 20
Mean cell hemoglobin concentra- tion	0-9	105	32 28 \pm 0 13	\pm 1 35			
	10-14	130	32 24 \pm 0 09	\pm 1 07			
	15-19	99	32 49 \pm 0 14	\pm 1 35	73	31 94 \pm 0 14	\pm 1 22
	20-39	43	32 55 \pm 0 25	\pm 1 62	77	31 76 \pm 0 17	\pm 1 48
	40 and above	75	31 99 \pm 0 19	\pm 1 64	64	31 87 \pm 0 17	\pm 1 37
Leukocyte count	0-9	100	12,570 \pm 312	\pm 3,124			
	10-14	112	9,973 \pm 206	\pm 2,177			
	15-19	101	9,926 \pm 245	\pm 2,467	84	9,655 \pm 262	\pm 2,402
	20-39	52	8,942 \pm 277	\pm 1,995	95	9,415 \pm 267	\pm 2,607
	40 and above	88	9,284 \pm 240	\pm 2,251	75	8,500 \pm 223	\pm 1,972
Neutrophils	0-9	100	48 80 \pm 0 82	\pm 8 19			
	10-14	112	50 36 \pm 0 79	\pm 8 35			
	15-19	101	54 78 \pm 0 79	\pm 7 96	84	61 19 \pm 0 87	\pm 7 98
	20-39	52	56 83 \pm 1 22	\pm 8 78	95	57 13 \pm 0 94	\pm 9 21
	40 and above	88	57 11 \pm 1 05	\pm 9 97	75	56 45 \pm 0 90	\pm 7 83
Lymphocytes	0-9	100	32 89 \pm 0 70	\pm 6 98			
	10-14	112	33 21 \pm 0 75	\pm 7 89			
	15-19	101	28 14 \pm 0 56	\pm 5 67	84	25 96 \pm 0 72	\pm 6 00
	20-39	52	26 59 \pm 0 94	\pm 6 79	95	27 09 \pm 0 67	\pm 6 66
	40 and above	88	28 89 \pm 0 90	\pm 8 53	75	30 33 \pm 0 81	\pm 7 02
Monocytes	0-9	100	6 57 \pm 0 21	\pm 2 08			
	10-14	112	6 20 \pm 0 18	\pm 1 89			
	15-19	101	6 64 \pm 0 23	\pm 2 36	84	5 70 \pm 0 22	\pm 2 03
	20-39	52	6 29 \pm 0 25	\pm 1 79	95	6 30 \pm 0 24	\pm 2 37
	40 and above	88	6 88 \pm 0 32	\pm 3 02	75	6 17 \pm 0 23	\pm 2 03
Eosinophils	0-9	100	11 58 \pm 0 79	\pm 7 89			
	10-14	112	10 07 \pm 0 67	\pm 7 09			
	15-19	101	10 49 \pm 0 78	\pm 7 91	84	7 51 \pm 0 60	\pm 5 51
	20-39	52	10 48 \pm 1 16	\pm 8 37	95	9 60 \pm 0 76	\pm 7 52
	40 and above	88	7 06 \pm 0 45	\pm 4 24	75	6 91 \pm 0 55	\pm 4 83
Plasma protein value	0-9	136	7 46 \pm 0 04	\pm 0 48			
	10-14	187	7 49 \pm 0 04	\pm 0 50			
	15-19	118	7 64 \pm 0 04	\pm 0 46	157	7 69 \pm 0 04	\pm 0 48
	20-39	51	7 5 \pm 0 03	\pm 0 57	96	7 78 \pm 0 05	\pm 0 48
	40 and above	90	7 57 \pm 0 05	\pm 0 48	77	7 70 \pm 0 06	\pm 0 53
Reticulocyte count	0-9	7	0 84 \pm 0 14	\pm 0 37			
	10-14	11	0 85 \pm 0 09	\pm 0 31			
	15-19	25	0 73 \pm 0 06	\pm 0 28	28	1 10 \pm 0 05	\pm 0 29
	20-39	15	1 11 \pm 0 10	\pm 0 40	14	0 92 \pm 0 11	\pm 0 41
	40 and above	16	0 75 \pm 0 08	\pm 0 32	17	0 72 \pm 0 07	\pm 0 28

* In this and the subsequent table, data for subjects under 14 are not differentiated according to sex

Control and Epilated Subjects Mean Values and Differences Between Means

Subject in Hiroshima						Mean Difference \pm Standard Error	
Male			Female			Male Subjects	Female Subjects
Number	Mean and Standard Error	Standard Deviation	Number	Mean and Standard Error	Standard Deviation		
85	4,676,000 \pm 38,000	\pm 346,000				+ 38,000 \pm 54,000	
79	4,682,000 \pm 39,000	\pm 346,000				- 36,000 \pm 50,000	
94	4,898,000 \pm 46,000	\pm 447,000				- 16,000 \pm 59,000	+169,000 \pm 66,000
46	4,813,000 \pm 72,000	\pm 490,000	106	4,464,000 \pm 41,000	\pm 346,000	- 9,000 \pm 89,000	+163,000 \pm 64,000
74	4,408,000 \pm 61,000	\pm 529,000	73	4,081,000 \pm 48,000	\pm 410,000	+154,000 \pm 78,000	+107,000 \pm 64,000
127	12 34 \pm 0 077	\pm 0 87				+0 31 \pm 0 12	
150	12 55 \pm 0 082	\pm 1 00				+0 31 \pm 0 10	
140	13 73 \pm 0 112	\pm 1 32	155	12 78 \pm 0 084	\pm 1 05	+0 46 \pm 0 15	+0 18 \pm 0 12
47	14 47 \pm 0 193	\pm 1 32	107	12 21 \pm 0 118	\pm 1 22	-0 02 \pm 0 23	+0 38 \pm 0 17
73	13 39 \pm 0 165	\pm 1 41	73	12 03 \pm 0 155	\pm 1 32	+0 55 \pm 0 22	+0 23 \pm 0 20
120	38 63 \pm 0 23	\pm 2 53				+0 48 \pm 0 32	
143	39 35 \pm 0 25	\pm 3 00				+0 58 \pm 0 29	
135	43 28 \pm 0 30	\pm 3 46	122	40 78 \pm 0 24	\pm 2 65	+0 77 \pm 0 44	+0 15 \pm 0 33
36	46 00 \pm 0 51	\pm 3 04	85	40 24 \pm 0 38	\pm 3 46	+0 14 \pm 0 67	+0 43 \pm 0 55
57	43 90 \pm 0 56	\pm 4 20	59	39 86 \pm 0 44	\pm 3 39	+1 18 \pm 0 71	+0 02 \pm 0 62
81	83 40 \pm 0 56	\pm 5 00				-0 17 \pm 0 78	
77	84 40 \pm 0 60	\pm 5 29				+0 66 \pm 0 81	
90	84 18 \pm 0 60	\pm 5 66	62	88 13 \pm 0 72	\pm 5 66	+3 97 \pm 0 88	-1 25 \pm 1 06
36	91 33 \pm 0 94	\pm 5 66	84	90 57 \pm 0 82	\pm 7 48	-0 33 \pm 1 29	-1 49 \pm 1 55
57	91 72 \pm 0 96	\pm 7 21	59	92 39 \pm 1 01	\pm 7 75	-1 50 \pm 1 26	-2 26 \pm 1 26
85	26 76 \pm 0 24	\pm 2 24				+0 09 \pm 0 30	
79	27 17 \pm 0 23	\pm 2 00				+0 51 \pm 0 29	
94	28 23 \pm 0 23	\pm 2 24	71	28 65 \pm 0 25	\pm 2 12	+1 02 \pm 0 30	-0 41 \pm 0 33
46	29 06 \pm 0 34	\pm 2 33	106	28 97 \pm 0 24	\pm 2 52	+0 21 \pm 0 43	-0 22 \pm 0 35
73	30 36 \pm 0 31	\pm 2 65	73	29 38 \pm 0 30	\pm 2 54	+0 31 \pm 0 38	-0 02 \pm 0 39
120	32 11 \pm 0 12	\pm 1 26				+0 17 \pm 0 18	
143	32 09 \pm 0 13	\pm 1 50				+0 15 \pm 0 16	
135	32 43 \pm 0 13	\pm 1 55	122	31 94 \pm 0 12	\pm 1 32	+0 06 \pm 0 19	-0 00 \pm 0 18
36	33 33 \pm 0 17	\pm 1 04	85	32 00 \pm 0 15	\pm 1 41	-0 78 \pm 0 30	-0 24 \pm 0 23
57	32 11 \pm 0 22	\pm 1 66	59	32 08 \pm 0 16	\pm 1 22	-0 12 \pm 0 29	-0 21 \pm 0 23
87	12,305 \pm 386	\pm 3,606				+ 270 \pm 500	
79	11,791 \pm 363	\pm 3,226				-1,820 \pm 420	
95	10,394 \pm 303	\pm 2,956	84	9,338 \pm 267	\pm 2,449	- 460 \pm 400	+320 \pm 370
47	9,053 \pm 342	\pm 2,347	105	8,481 \pm 218	\pm 2,236	- 110 \pm 440	+940 \pm 350
73	8,555 \pm 274	\pm 2,338	75	8,233 \pm 258	\pm 2,236	+ 720 \pm 360	+270 \pm 350
87	49 53 \pm 1 07	\pm 10 00				-0 73 \pm 1 35	
79	51 19 \pm 1 01	\pm 9 02				-0 83 \pm 1 28	
95	52 64 \pm 1 09	\pm 10 61	84	58 13 \pm 1 13	\pm 10 31	+2 14 \pm 1 35	+3 06 \pm 1 43
45	56 58 \pm 1 30	\pm 8 75	103	57 34 \pm 0 85	\pm 8 66	+0 25 \pm 1 78	-0 21 \pm 1 27
71	57 76 \pm 1 03	\pm 8 66	73	57 76 \pm 0 97	\pm 8 29	-0 65 \pm 1 47	-1 28 \pm 1 32
87	32 14 \pm 0 89	\pm 8 29				+0 75 \pm 1 13	
79	30 11 \pm 0 89	\pm 7 91				+3 10 \pm 1 16	
95	27 46 \pm 0 81	\pm 7 91	84	26 46 \pm 0 75	\pm 6 91	+0 68 \pm 0 98	-0 50 \pm 1 04
45	27 08 \pm 1 12	\pm 7 48	103	26 15 \pm 0 74	\pm 7 46	-0 49 \pm 1 46	+0 94 \pm 1 00
71	26 64 \pm 0 77	\pm 6 51	73	28 10 \pm 0 93	\pm 7 91	+1 95 \pm 1 18	+2 23 \pm 1 23
87	6 06 \pm 0 23	\pm 2 10				+0 51 \pm 0 31	
79	6 42 \pm 0 27	\pm 2 37				-0 22 \pm 0 32	
95	6 30 \pm 0 22	\pm 2 17	84	5 70 \pm 0 23	\pm 2 06	+0 34 \pm 0 32	-0 00 \pm 0 32
45	6 63 \pm 0 34	\pm 2 29	103	6 14 \pm 0 22	\pm 2 25	-0 34 \pm 0 42	+0 16 \pm 0 33
71	7 20 \pm 0 33	\pm 2 75	73	6 54 \pm 0 31	\pm 2 65	-0 32 \pm 0 46	-0 37 \pm 0 39
87	12 08 \pm 0 89	\pm 8 29				-0 50 \pm 1 19	
79	12 14 \pm 0 83	\pm 7 39				-2 07 \pm 1 07	
95	13 93 \pm 1 09	\pm 10 61	84	9 79 \pm 0 83	\pm 7 64	-3 44 \pm 1 34	-2 28 \pm 1 02
45	9 34 \pm 1 11	\pm 7 42	103	10 21 \pm 0 73	\pm 7 37	+1 14 \pm 1 61	-0 61 \pm 1 05
71	8 72 \pm 0 66	\pm 5 55	73	8 34 \pm 0 70	\pm 6 04	-1 66 \pm 0 80	-1 43 \pm 0 89
127	7 52 \pm 0 05	\pm 0 57				-0 06 \pm 0 06	
150	7 64 \pm 0 04	\pm 0 53				-0 15 \pm 0 06	
140	7 85 \pm 0 04	\pm 0 49	155	7 78 \pm 0 04	\pm 0 53	-0 21 \pm 0 06	-0 09 \pm 0 06
47	7 63 \pm 0 09	\pm 0 59	107	7 61 \pm 0 05	\pm 0 54	-0 13 \pm 0 12	+0 17 \pm 0 07
73	7 37 \pm 0 06	\pm 0 53	73	7 63 \pm 0 06	\pm 0 50	+0 20 \pm 0 08	+0 07 \pm 0 08
11	0 92 \pm 0 17	\pm 0 56				-0 08 \pm 0 22	
17	0 90 \pm 0 10	\pm 0 43				-0 05 \pm 0 13	
20	0 84 \pm 0 12	\pm 0 54	16	1 38 \pm 0 17	\pm 0 68	-0 11 \pm 0 13	-0 28 \pm 0 18
10	1 06 \pm 0 13	\pm 0 42	18	0 95 \pm 0 09	\pm 0 37	+0 05 \pm 0 16	-0 02 \pm 0 14
14	0 79 \pm 0 07	\pm 0 25	14	0 89 \pm 0 10	\pm 0 36	-0 04 \pm 0 11	-0 17 \pm 0 12

these findings will not be discussed at this time but will be considered in another paper ²⁷ It is apparent from the tables that there was no clear and consistent tendency for any particular age or sex group to contribute disproportionately to the observed differences in erythrocyte count, hemoglobin content and hematocrit

TABLE 4—*Relation Between Age and Sex and Hematologic Findings Comparison of Mean Differences of Established Pairs, Grouped According to Age and Sex*

Observation	Age, Years	Male Subjects		Female Subjects	
		Number	Mean Difference and Standard Error	Number	Mean Difference and Standard Error
Erythrocyte count	0-9	55	+ 3,000 \pm 59,000		
	10-14	55	+ 3,000 \pm 69,000		
	15-19	91	- 45,000 \pm 66,000	42	+110,000 \pm 84,000
	20-39	31	-131,000 \pm 92,000	66	+114,000 \pm 81,000
	40 and above	49	+232,000 \pm 92,000	48	+210,000 \pm 70,000
Hemoglobin concentration	0-9	56	+0.29 \pm 0.167		
	10-14	55	+0.22 \pm 0.164		
	15-19	94	+0.24 \pm 0.160	42	+0.24 \pm 0.182
	20-39	32	-0.25 \pm 0.280	68	+0.28 \pm 0.221
	40 and above	51	+0.69 \pm 0.289	49	+0.27 \pm 0.250
Mean cell hemoglobin	0-9	55	+0.46 \pm 0.312		
	10-14	55	+0.50 \pm 0.357		
	15-19	94	+0.71 \pm 0.254	40	-0.30 \pm 0.396
	20-39	31	-0.05 \pm 0.454	65	+0.04 \pm 0.371
	40 and above	49	-0.13 \pm 0.446	47	-0.59 \pm 0.455
Leukocyte count	0-9	71	+ 218 \pm 566		
	10-14	61	-1,484 \pm 499		
	15-19	87	- 604 \pm 379	39	- 64 \pm 533
	20-39	29	- 155 \pm 596	68	+1,427 \pm 399
	40 and above	52	+ 320 \pm 374	51	+ 500 \pm 396
Neutrophils	0-9	60	-1.87 \pm 1.77		
	10-14	55	-1.27 \pm 1.81		
	15-19	79	-1.29 \pm 1.43	37	+4.59 \pm 2.18
	20-39	30	+0.40 \pm 2.15	69	+0.14 \pm 1.59
	40 and above	52	-0.85 \pm 1.93	51	-2.00 \pm 1.77
Lymphocytes	0-9	60	+2.33 \pm 1.44		
	10-14	55	+1.55 \pm 1.46		
	15-19	79	+1.76 \pm 1.07	37	+1.65 \pm 1.53
	20-39	30	+0.07 \pm 1.68	69	+1.12 \pm 1.15
	40 and above	52	+2.88 \pm 1.47	51	+3.90 \pm 1.49
Monocytes	0-9	60	+0.88 \pm 0.35		
	10-14	55	-0.06 \pm 0.40		
	15-19	79	+0.07 \pm 0.31	37	-0.61 \pm 0.42
	20-39	30	-0.43 \pm 0.54	69	+0.38 \pm 0.42
	40 and above	52	-0.75 \pm 0.42	51	-0.15 \pm 0.42
Eosinophils	0-9	60	-1.40 \pm 1.60		
	10-14	55	-0.53 \pm 1.15		
	15-19	79	-0.34 \pm 1.23	37	-3.86 \pm 1.70
	20-39	30	+1.33 \pm 1.49	69	-0.88 \pm 1.09
	40 and above	52	-0.81 \pm 1.15	51	-2.41 \pm 1.18
Plasma protein value	0-9	56	-0.09 \pm 0.07		
	10-14	56	-0.18 \pm 0.08		
	15-19	94	-0.16 \pm 0.06	42	+0.07 \pm 0.10
	20-39	32	-0.05 \pm 0.09	67	+0.18 \pm 0.07
	40 and above	49	+0.18 \pm 0.09	49	-0.01 \pm 0.05

value Rather, the over-all difference for these determinations seems to be due to contributions from most of the groups studied Thus, in table 4, for instance,

27 Snell, F M Observations on the Hematological Values of the Japanese, to be published

six of the eight differences in erythrocyte count and seven of the eight differences in hemoglobin content agree in sign with that for the group as a whole. There were, however, a few apparently disproportionate responses of particular sex and

TABLE 5—*Relation Between Extent of Associated Traumatic Injury and Burns and Hematologic Findings for Epilated Persons Comparison of Mean Values According to Extent of Injury*

Observation	Subjects in Group 1 *		Subjects in Group 2		Subjects in Group 3	
	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error
Erythrocyte count	197	4,524,000 \pm 36,000	294	4,512,000 \pm 29,000	89	4,574,000 \pm 50,000
Hemoglobin concentration	302	12.80 \pm 0.079	411	12.78 \pm 0.065	105	12.96 \pm 0.137
Hematocrit reading	268	40.66 \pm 0.232	353	41.08 \pm 0.199	93	41.41 \pm 0.384
Mean cell volume	174	87.48 \pm 0.528	254	88.69 \pm 0.472	76	88.42 \pm 0.733
Mean cell hemoglobin	196	28.44 \pm 0.175	294	28.51 \pm 0.157	89	28.28 \pm 0.252
Mean cell hemoglobin concentration	268	32.33 \pm 0.091	352	32.15 \pm 0.074	93	32.07 \pm 0.164
Leukocyte count	199	10,394 \pm 228	296	9,689 \pm 179	88	9,477 \pm 319
Neutrophils	196	53.80 \pm 0.736	294	54.70 \pm 0.601	86	55.29 \pm 1.009
Lymphocytes	196	28.16 \pm 0.572	294	28.12 \pm 0.461	86	27.53 \pm 0.824
Monocytes	196	6.35 \pm 0.163	294	6.42 \pm 0.146	86	6.41 \pm 0.217
Eosinophils	196	11.51 \pm 0.519	294	10.94 \pm 0.484	86	10.18 \pm 0.894
Plasma protein value	302	7.67 \pm 0.032	411	7.63 \pm 0.027	105	7.64 \pm 0.050
Reticulocyte count	37	0.934 \pm 0.069	58	0.922 \pm 0.065	17	0.874 \pm 0.070

* In this and the subsequent table, group 1 indicates those persons with no injuries, or with minor burns and glass cuts, group 2, those with moderately severe first, second or third degree burns involving up to approximately 10 per cent of the body area, or with comparable other traumatic injury, and group 3, those with burns involving more than 10 per cent of the body area, or with other types of severe traumatic injury.

TABLE 6—*Relation Between Extent of Associated Traumatic Injury and Burns and Hematologic Findings for Epilated Persons Comparison of Mean Differences Between Established Pairs According to Extent of Injury of Epilated Subjects*

Observation	Subjects in Group 1		Subjects in Group 2		Subjects in Group 3	
	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error
Erythrocyte count	135	+154,000 \pm 51,000	214	+26,000 \pm 39,000	65	-47,000 \pm 65,000
Hemoglobin concentration	139	+0.46 \pm 0.138	216	+0.22 \pm 0.107	66	+0.23 \pm 0.180
Mean cell hemoglobin	135	+0.12 \pm 0.239	212	+0.22 \pm 0.192	63	+0.72 \pm 0.306
Leukocyte count	143	+10 \pm 33	221	-20 \pm 237	66	-54 \pm 422
Neutrophils	133	+0.80 \pm 1.133	210	-1.52 \pm 0.924	66	-1.46 \pm 1.663
Lymphocytes	133	+1.93 \pm 0.862	210	+1.82 \pm 0.716	66	+2.00 \pm 1.322
Monocytes	133	-0.17 \pm 0.256	210	+0.12 \pm 0.220	66	+0.36 \pm 0.341
Eosinophils	133	-2.20 \pm 0.863	210	-0.44 \pm 0.659	66	-0.61 \pm 1.181
Plasma protein value	139	-0.07 \pm 0.05	214	+0.22 \pm 0.038	66	+0.17 \pm 0.088

age groups, which, taken at their face value, are statistically significant. It should be borne in mind that on the basis of chance alone values in 5 per cent of *t* tests may be expected to exceed the value of 2.0. This variation also occurred in determination of the cell constants, even though there was no significant over-all tendency. The fact that the two different analytic approaches failed in many instances to yield confirming results lessens the weight to be given to these findings.

The total leukocyte count and the percentage of neutrophils and monocytes, which showed no significant gross differences in table 2, likewise showed no clearly consistent tendencies on the breakdown, although there were several minor differences which may, in the light of future research, prove significant. The decrease in percentage of lymphocytes and the increase in percentage of eosinophils recorded in Hiroshima apparently occurred in groups of all ages and both sexes. Differences in plasma protein values, although statistically significant in many of the groups, fell into no simple pattern. Reticulocyte counts, likewise, showed no significant pattern.

Relation Between Traumatic Injuries and Flash Burns and Hematologic Observations—As noted previously, many epilated subjects received, in addition to the radiation, flash burns, glass cuts and injuries from other flying debris. The possibility that the observed differences between subjects in Kure and those in Hiroshima were actually due to these associated injuries rather than to the factor of irradiation had to be explored. Accordingly, Hiroshima subjects were classified into three groups, group 1 consisting of those persons with no injuries or with minor burns and glass cuts, group 2 consisting of those with moderately severe first, second or third degree burns involving up to approximately 10 per cent of the body area, or with roughly comparable other traumatic injury, and group 3 consisting of those who received either burns of varying severity involving more than 10 per cent of the body area or other types of severe traumatic injury. The records of relatively few persons, who could not be readily classified from the available data, were not incorporated into the analysis. The mean values in these three groups, and the mean differences between the established pairs, are shown in tables 5 and 6.

The significance of the various trends shown here has been investigated by an analysis of the variance between and within groups. There was a tendency for the erythrocyte count to be higher for those subjects who received the severest injuries. This tendency is evident in both table 5 and table 6 but is statistically significant only in table 6. Moreover, inspection of tables 5 and 6 reveals that values for hemoglobin concentration and hematocrit reading tend to vary in the same manner as do those for erythrocyte count, although the trend is not statistically significant by this analysis. One faces, then, the paradox that those persons most severely burned or otherwise injured at the time of the bombing later showed a tendency to an increased number of erythrocytes, with correspondingly higher values for hemoglobin concentration and hematocrit reading. This point will be discussed further later in this report. The explanation of the over-all differences between subjects in Kure and those in Hiroshima does not lie here.

In table 5 there is indicated a tendency to a lower leukocyte count for those receiving the severest injury, but this tendency, although statistically significant in table 5, is not borne out in table 6, therefore, its validity may be questioned.

Relation Between Amount of Radiation and Hematologic Observations—Although all the subjects in Hiroshima included in this study allegedly experienced scalp epilation, which is probably the most reliable single criterion of the absorption of large amounts of whole body radiation, there undoubtedly existed, within the group, considerable variation in the actual dose received, which may have varied from the minimal epilating dose with this type of irradiation (about 300 r) up to the maximum tolerated by a few persons (say 700 r). Moreover, it is likely that a few persons included in the study did not experience true radiation

epilation One hundred and ninety-three of 924 persons, or 20.9 per cent of those reporting epilation, were more than 2 kilometers from the hypocenter at the time of the explosion, whereas the Joint Commission found that only 8.3 per cent of the cases of epilation which they studied in the weeks immediately following the bombing were in persons who had been beyond the 2 kilometer zone¹ How-

TABLE 7—*Relation Between Distance from Hypocenter and Hematologic Findings Comparison of Mean Values According to Distance*

Observation	Distance from Hypocenter					
	0 to 1 Km		1 to 2 Km		Over 2 Km	
	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error
Erythrocyte count	135	4,429,000 \pm 47,000	378	4,530,000 \pm 25,000	116	4,610,000 \pm 44,000
Hemoglobin concentration	169	12.89 \pm 0.113	518	12.85 \pm 0.058	186	12.77 \pm 0.096
Hematoerit reading	138	41.38 \pm 0.318	440	41.07 \pm 0.178	169	40.80 \pm 0.298
Mean cell volume	108	89.46 \pm 0.745	328	88.46 \pm 0.382	108	86.69 \pm 0.618
Mean cell hemoglobin	135	28.96 \pm 0.265	377	28.57 \pm 0.122	121	27.97 \pm 0.225
Mean cell hemoglobin concentration	138	32.44 \pm 0.132	440	32.19 \pm 0.063	168	32.05 \pm 0.119
Leukocyte count	135	9,966 \pm 277	393	9,706 \pm 156	116	10,552 \pm 299
Neutrophils	133	53.82 \pm 0.840	390	55.52 \pm 0.490	115	54.03 \pm 0.961
Lymphocytes	133	26.55 \pm 0.603	390	28.30 \pm 0.389	115	29.01 \pm 0.844
Monocytes	133	6.42 \pm 0.213	390	6.30 \pm 0.119	115	6.41 \pm 0.228
Eosinophils	133	13.07 \pm 0.782	390	10.02 \pm 0.360	115	9.97 \pm 0.689
Plasma protein value	169	7.66 \pm 0.051	518	7.63 \pm 0.023	186	7.71 \pm 0.039
Reticulocyte count	27	0.857 \pm 0.097	64	0.975 \pm 0.038	29	0.981 \pm 0.109

TABLE 8—*Relation Between Distance from Hypocenter and Hematologic Findings Comparison of Mean Difference Between Established Pairs According to Distance*

Observation	Distance from Hypocenter					
	0 to 1 Km		1 to 2 Km		Over 2 Km	
	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error
Erythrocyte count	93	+212,000 \pm 65,000	256	+17,000 \pm 33,000	88	-3,000 \pm 65,000
Hemoglobin concentration	92	+0.64 \pm 0.154	264	+0.92 \pm 0.100	90	+0.48 \pm 0.146
Mean cell hemoglobin	92	-0.20 \pm 0.305	250	+0.44 \pm 0.152	88	+0.97 \pm 0.289
Leukocyte count	91	-489 \pm 417	277	+323 \pm 214	88	-852 \pm 357
Neutrophils	83	-0.02 \pm 1.427	266	-0.59 \pm 0.834	84	-1.05 \pm 1.32
Lymphocytes	83	+3.05 \pm 1.070	266	+1.23 \pm 0.640	84	+1.86 \pm 0.990
Monocytes	83	+0.09 \pm 0.314	266	-0.00 \pm 0.180	84	+0.20 \pm 0.349
Eosinophils	83	-2.11 \pm 1.178	266	-0.48 \pm 0.573	84	-1.00 \pm 0.988
Plasma protein value	92	-0.10 \pm 0.063	264	+0.04 \pm 0.036	90	-0.12 \pm 0.057

ever, the two studies are not entirely comparable. In order to analyze the possibility that those subjects who received the most radiation contributed disproportionately to the observed differences in the two series, the data have been broken down in three different ways. In tables 7 and 8, the data are presented in terms of the subject's distance from the hypocenter of the explosion, with individual subjects classified as to whether they were within 1 kilometer, between 1 and 2 kilometers, or beyond 2 kilometers at the time of the explosion. No attempt has been made in this analysis to evaluate further the shielding factor. In tables

9 and 10, the data are presented in terms of the extent of scalp epilation reported by the subject, three grades of epilation were established, corresponding to loss of under one third of the hair, loss of between one third and two thirds, and loss of over two thirds. Finally, in tables 11 and 12, the data have been analyzed according to the reported symptomatologic severity of the radiation sickness, as

TABLE 9—*Relation Between Extent of Epilation and Hematologic Findings Comparison of Mean Values*

Observation	Subjects with Grade 1 Epilation *		Subjects with Grade 2 Epilation		Subjects with Grade 3 Epilation	
	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error
Erythrocyte count	296	4,542,000 \pm 28,000	116	4,607,000 \pm 45,000	200	4,464,000 \pm 37,000
Hemoglobin concentration	432	12.77 \pm 0.064	159	13.06 \pm 0.105	266	12.79 \pm 0.092
Hematocrit reading	383	40.87 \pm 0.191	135	41.43 \pm 0.310	223	40.94 \pm 0.263
Mean cell volume	265	88.14 \pm 0.443	102	88.24 \pm 0.714	164	88.34 \pm 0.605
Mean cell hemoglobin	295	28.43 \pm 0.142	120	28.63 \pm 0.224	200	28.56 \pm 0.200
Mean cell hemoglobin concentration	382	32.07 \pm 0.02	135	32.32 \pm 0.122	223	32.35 \pm 0.106
Leukocyte count	300	10,046 \pm 202	120	9,836 \pm 242	202	9,550 \pm 211
Neutrophils	300	54.52 \pm 0.60	120	55.98 \pm 0.82	200	54.61 \pm 0.73
Lymphocytes	300	28.80 \pm 0.46	120	27.31 \pm 0.69	200	27.16 \pm 0.53
Monocytes	300	6.42 \pm 0.14	120	5.98 \pm 0.20	200	6.53 \pm 0.17
Eosinophils	300	10.24 \pm 0.41	120	10.79 \pm 0.76	200	11.69 \pm 0.64
Plasma protein value	432	7.64 \pm 0.025	159	7.68 \pm 0.042	266	7.66 \pm 0.037
Reticulocyte count	54	0.968 \pm 0.066	29	0.902 \pm 0.081	35	0.930 \pm 0.068

* In this and the subsequent table, grade 1 epilation indicates loss of under one third of the hair, grade 2, loss of between one third and two thirds, and grade 3, loss of over two thirds.

TABLE 10—*Relation Between Extent of Epilation and Hematologic Findings Comparison of Mean Difference Between Established Pairs*

Observation	Subjects with Grade 1 Epilation		Subjects with Grade 2 Epilation		Subjects with Grade 3 Epilation	
	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error
Erythrocyte count	205	+37,000 \pm 42,000	83	+25,000 \pm 64,000	142	+107,000 \pm 50,000
Hemoglobin concentration	209	+0.22 \pm 0.110	86	+0.10 \pm 0.166	143	+0.44 \pm 0.135
Mean cell hemoglobin	204	+0.19 \pm 0.189	82	+0.26 \pm 0.290	141	+0.15 \pm 0.242
Leukocyte count	221	+120 \pm 256	87	-548 \pm 375	140	+21 \pm 304
Neutrophils	203	-0.29 \pm 0.974	87	-2.18 \pm 1.373	134	+0.15 \pm 1.072
Lymphocytes	203	+0.95 \pm 0.714	87	+2.66 \pm 1.175	134	+2.56 \pm 0.823
Monocytes	203	+0.19 \pm 0.214	87	+0.52 \pm 0.281	134	-0.55 \pm 0.255
Eosinophils	203	-0.85 \pm 0.652	87	-0.79 \pm 1.155	134	-1.40 \pm 0.876
Plasma protein value	209	-0.04 \pm 0.038	86	-0.05 \pm 0.070	143	+0.02 \pm 0.051

judged by the cocurrence of nausea, anorexia, malaise, vomiting, gingivitis, diarrhea, pharyngitis, petechiae and purpura. Grade 1 includes those persons with nausea and/or anorexia, grade 2, those with vomiting and/or malaise, with or without the symptoms of grade 1, grade 3, those with gingivitis and/or diarrhea, with or without the symptoms of grades 1 or 2, and grade 4, those with pharyngitis, petechiae and/or purpura, with or without the signs and symptoms of grades 1, 2 or 3. In all three analyses (tables 7 through 12) available data for

a few individual subjects, not readily classifiable, have been omitted. This is admittedly a rough classification at the best, but it probably is as satisfactory as possible under the circumstances. A statistical analysis revealed, as might have

TABLE 11—*Relation Between Severity of Radiation Sickness and Hematologic Findings*
Comparison of Mean Values

Observation	Subjects with Grade 1 Radiation Sickness *		Subjects with Grade 2 Radiation Sickness		Subjects with Grade 3 Radiation Sickness		Subjects with Grade 4 Radiation Sickness	
	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error
Erythrocyte count	43	4,556,000 \pm 61,000	87	4,578,000 \pm 48,000	201	4,592,000 \pm 33,000	290	4,460,000 \pm 31,000
Hemoglobin concentration	97	12.12 \pm 0.110	137	12.87 \pm 0.098	260	12.90 \pm 0.079	358	12.90 \pm 0.077
Hematocrit reading	90	39.06 \pm 0.350	127	40.96 \pm 0.307	209	41.20 \pm 0.268	313	41.44 \pm 0.219
Mean cell volume	39	86.59 \pm 1.06	86	87.91 \pm 0.65	175	87.11 \pm 0.52	246	89.70 \pm 0.49
Mean cell hemoglobin	43	27.76 \pm 0.338	94	28.32 \pm 0.262	200	28.11 \pm 0.174	291	29.03 \pm 0.157
Mean cell hemoglobin concentration	86	31.72 \pm 0.152	127	32.08 \pm 0.109	209	31.62 \pm 0.093	313	32.36 \pm 0.101
Leukocyte count	45	10,811 \pm 516	98	10,102 \pm 317	210	9,795 \pm 229	288	9,656 \pm 170
Neutrophils	43	53.75 \pm 1.69	97	54.11 \pm 1.02	208	54.82 \pm 0.65	278	55.56 \pm 0.62
Lymphocytes	43	28.40 \pm 1.15	97	28.90 \pm 0.74	208	28.56 \pm 0.54	278	27.04 \pm 0.47
Monocytes	43	6.13 \pm 0.28	97	6.44 \pm 0.26	208	6.25 \pm 0.17	278	6.42 \pm 0.14
Eosinophils	43	11.99 \pm 1.19	97	9.91 \pm 0.80	208	9.29 \pm 0.44	278	10.17 \pm 0.47
Plasma protein value	97	7.54 \pm 0.059	146	7.69 \pm 0.04	260	7.65 \pm 0.034	358	7.67 \pm 0.029
Reticulocyte count	8	1.175 \pm 0.122	21	1.236 \pm 0.113	32	0.844 \pm 0.088	55	0.879 \pm 0.055

* In this and the subsequent table, grade 1 sickness indicates nausea and/or anorexia, grade 2, vomiting and/or malaise, with or without the symptoms of grade 1, grade 3, gingivitis and/or diarrhea, with or without the symptoms of grades 1 or 2, and grade 4, pharyngitis, petechiae and/or purpura, with or without the symptoms of grade 1, 2 or 3.

TABLE 12—*The Relation Between Severity of Radiation Sickness and Hematological Findings*
Comparison of Mean Differences Between Established Pairs

Observation	Subjects with Grade 1 Radiation Sickness		Subjects with Grade 2 Radiation Sickness		Subjects with Grade 3 Radiation Sickness		Subjects with Grade 4 Radiation Sickness	
	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error
Erythrocyte count	25	+25,000 \pm 110,000	68	+25,000 \pm 62,000	128	-11,000 \pm 46,000	218	+110,000 \pm 43,000
Hemoglobin concentration	26	+0.36 \pm 0.242	68	+0.01 \pm 0.154	132	+0.22 \pm 0.135	221	+0.38 \pm 0.113
Mean cell hemoglobin	25	+0.46 \pm 0.601	65	-0.22 \pm 0.340	127	+0.65 \pm 0.235	217	-0.04 \pm 0.183
Leukocyte count	34	+30 \pm 718	72	-218 \pm 461	129	+120 \pm 324	221	-106 \pm 230
Neutrophils	31	-1.74 \pm 2.439	72	+1.28 \pm 1.608	120	-0.35 \pm 1.128	210	-1.14 \pm 0.920
Lymphocytes	31	+3.26 \pm 1.909	72	-0.79 \pm 1.182	120	+1.47 \pm 0.879	210	+2.81 \pm 0.703
Monocytes	31	+0.60 \pm 0.476	72	-0.21 \pm 0.299	120	-0.06 \pm 0.283	210	+0.07 \pm 0.216
Eosinophils	31	-1.97 \pm 1.606	72	+0.03 \pm 1.331	120	-0.95 \pm 0.829	210	-1.31 \pm 0.669
Plasma protein value	26	-0.02 \pm 0.112	68	-0.10 \pm 0.076	132	+0.08 \pm 0.050	221	-0.05 \pm 0.039

been expected, a high degree of positive association between these criteria for estimating the relative amount of radiation.

From a study of tables 7 through 12, three observations of some possible significance emerge.

1 The erythrocyte count showed a uniform tendency, as indicated in all these tables, to be lower in the groups presumably receiving the most radiation, whether

9 and 10, the data are presented in terms of the extent of scalp epilation reported by the subject, three grades of epilation were established, corresponding to loss of under one third of the hair, loss of between one third and two thirds, and loss of over two thirds. Finally, in tables 11 and 12, the data have been analyzed according to the reported symptomatologic severity of the radiation sickness, as

TABLE 9—*Relation Between Extent of Epilation and Hematologic Findings Comparison of Mean Values*

Observation	Subjects with Grade 1 Epilation *		Subjects with Grade 2 Epilation		Subjects with Grade 3 Epilation	
	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error
Erythrocyte count	296	4,542,000 \pm 28,000	116	4,607,000 \pm 45,000	200	4,464,000 \pm 37,000
Hemoglobin concentration	432	12.77 \pm 0.064	159	13.06 \pm 0.105	266	12.79 \pm 0.092
Hematocrit reading	383	40.87 \pm 0.191	135	41.43 \pm 0.310	223	40.94 \pm 0.263
Mean cell volume	265	88.14 \pm 0.443	102	88.24 \pm 0.714	164	88.34 \pm 0.605
Mean cell hemoglobin	295	28.43 \pm 0.142	120	28.63 \pm 0.224	200	28.56 \pm 0.200
Mean cell hemoglobin concentration	382	32.07 \pm 0.62	135	32.32 \pm 0.122	223	32.35 \pm 0.106
Leukocyte count	300	10,046 \pm 202	120	9,836 \pm 242	202	9,550 \pm 211
Neutrophils	300	54.52 \pm 0.60	120	55.98 \pm 0.82	200	54.61 \pm 0.73
Lymphocytes	300	28.80 \pm 0.46	120	27.31 \pm 0.69	200	27.16 \pm 0.53
Monocytes	300	6.42 \pm 0.14	120	5.98 \pm 0.20	200	6.53 \pm 0.17
Eosinophils	300	10.24 \pm 0.41	120	10.79 \pm 0.76	200	11.69 \pm 0.64
Plasma protein value	432	7.64 \pm 0.025	159	7.68 \pm 0.042	266	7.66 \pm 0.037
Reticulocyte count	54	0.968 \pm 0.006	29	0.902 \pm 0.081	15	0.930 \pm 0.068

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	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error
Erythrocyte count	205	+37,000 \pm 42,000	83	+25,000 \pm 64,000	142	+107,000 \pm 50,000
Hemoglobin concentration	209	+0.22 \pm 0.110	86	+0.10 \pm 0.166	143	+0.44 \pm 0.135
Mean cell hemoglobin	204	+0.19 \pm 0.189	82	+0.26 \pm 0.290	141	+0.15 \pm 0.242
Leukocyte count	221	+120 \pm 256	87	-348 \pm 375	140	+21 \pm 304
Neutrophils	203	-0.29 \pm 0.974	87	-2.18 \pm 1.373	134	+0.15 \pm 1.072
Lymphocytes	203	+0.95 \pm 0.714	87	+2.66 \pm 1.175	134	+2.56 \pm 0.823
Monocytes	203	+0.19 \pm 0.214	87	+0.52 \pm 0.281	134	-0.55 \pm 0.255
Eosinophils	203	-0.85 \pm 0.652	87	-0.79 \pm 1.155	134	-1.40 \pm 0.876
Plasma protein value	209	-0.04 \pm 0.038	86	-0.05 \pm 0.070	143	+0.02 \pm 0.051

judged by the cocurrence of nausea, anorexia, malaise, vomiting, gingivitis, diarrhea, pharyngitis, petechiae and purpura. Grade 1 includes those persons with nausea and/or anorexia, grade 2, those with vomiting and/or malaise, with or without the symptoms of grade 1, grade 3, those with gingivitis and/or diarrhea, with or without the symptoms of grades 1 or 2, and grade 4, those with pharyngitis, petechiae and/or purpura, with or without the signs and symptoms of grades 1, 2 or 3. In all three analyses (tables 7 through 12) available data for

a few individual subjects, not readily classifiable, have been omitted. This is admittedly a rough classification at the best, but it probably is as satisfactory as possible under the circumstances. A statistical analysis revealed, as might have

TABLE 11—*Relation Between Severity of Radiation Sickness and Hematologic Findings*
Comparison of Mean Values

Observation	Subjects with Grade 1 Radiation Sickness *		Subjects with Grade 2 Radiation Sickness		Subjects with Grade 3 Radiation Sickness		Subjects with Grade 4 Radiation Sickness	
	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error	No	Mean and Standard Error
Erythrocyte count	43	4,556,000 \pm 61,000	87	4,578,000 \pm 48,000	201	4,592,000 \pm 33,000	290	4,460,000 \pm 31,000
Hemoglobin concentration	97	12.42 \pm 0.110	197	12.87 \pm 0.098	260	12.90 \pm 0.079	358	12.90 \pm 0.077
Hematocrit reading	90	39.66 \pm 0.350	127	40.96 \pm 0.307	209	41.20 \pm 0.268	313	41.44 \pm 0.219
Mean cell volume	39	86.59 \pm 1.06	86	87.91 \pm 0.65	175	87.11 \pm 0.52	246	89.70 \pm 0.49
Mean cell hemoglobin	43	27.76 \pm 0.338	94	28.32 \pm 0.262	200	28.11 \pm 0.174	291	29.03 \pm 0.157
Mean cell hemoglobin concentration	86	31.72 \pm 0.152	127	32.08 \pm 0.109	209	31.62 \pm 0.093	313	32.36 \pm 0.101
Leukocyte count	45	10,811 \pm 516	98	10,102 \pm 317	210	9,795 \pm 229	288	9,656 \pm 170
Neutrophils	43	53.75 \pm 1.69	97	51.11 \pm 1.02	208	54.82 \pm 0.65	278	55.56 \pm 0.62
Lymphocytes	43	28.40 \pm 1.15	97	28.90 \pm 0.74	208	28.56 \pm 0.54	278	27.04 \pm 0.47
Monocytes	43	6.13 \pm 0.28	97	6.44 \pm 0.26	208	6.25 \pm 0.17	278	6.42 \pm 0.14
Eosinophils	43	11.99 \pm 1.19	97	9.91 \pm 0.80	208	9.29 \pm 0.44	278	10.17 \pm 0.47
Plasma protein value	97	7.54 \pm 0.059	116	7.69 \pm 0.04	260	7.65 \pm 0.034	358	7.67 \pm 0.029
Reticulocyte count	8	1.175 \pm 0.122	21	1.236 \pm 0.113	32	0.844 \pm 0.088	55	0.879 \pm 0.055

* In this and the subsequent table, grade 1 sickness indicates nausea and/or anorexia, grade 2, vomiting and/or malaise, with or without the symptoms of grade 1, grade 3, gingivitis and/or diarrhea, with or without the symptoms of grades 1 or 2, and grade 4, pharyngitis, petechiae and/or purpura, with or without the symptoms of grade 1, 2 or 3.

TABLE 12—*The Relation Between Severity of Radiation Sickness and Hematological Findings*
Comparison of Mean Differences Between Established Pairs

Observation	Subjects with Grade 1 Radiation Sickness		Subjects with Grade 2 Radiation Sickness		Subjects with Grade 3 Radiation Sickness		Subjects with Grade 4 Radiation Sickness	
	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error	No	Mean Difference and Standard Error
Erythrocyte count	25	+25,000 \pm 110,000	68	+25,000 \pm 62,000	128	-11,000 \pm 46,000	218	+110,000 \pm 43,000
Hemoglobin concentration	26	+0.36 \pm 0.242	68	+0.01 \pm 0.154	132	+0.22 \pm 0.135	221	+0.38 \pm 0.113
Mean cell hemoglobin	25	+0.46 \pm 0.601	65	-0.22 \pm 0.340	127	+0.65 \pm 0.235	217	-0.04 \pm 0.183
Leukocyte count	34	+30 \pm 718	72	-218 \pm 461	129	+120 \pm 324	221	-106 \pm 230
Neutrophils	31	-1.74 \pm 2.439	72	+1.28 \pm 1.608	120	-0.35 \pm 1.128	210	-1.14 \pm 0.920
Lymphocytes	31	+3.26 \pm 1.909	72	-0.79 \pm 1.182	120	+1.47 \pm 0.879	210	+2.81 \pm 0.703
Monocytes	31	+0.60 \pm 0.476	72	-0.21 \pm 0.299	120	-0.06 \pm 0.283	210	+0.07 \pm 0.216
Eosinophils	31	-1.97 \pm 1.606	72	+0.03 \pm 1.331	120	-0.95 \pm 0.829	210	-1.31 \pm 0.669
Plasma protein value	26	-0.02 \pm 0.112	68	-0.10 \pm 0.076	132	+0.08 \pm 0.050	221	-0.05 \pm 0.039

been expected, a high degree of positive association between these criteria for estimating the relative amount of radiation.

From a study of tables 7 through 12, three observations of some possible significance emerge:

1. The erythrocyte count showed a uniform tendency, as indicated in all these tables, to be lower in the groups presumably receiving the most radiation, whether

judged by nearness to the hypocenter, by amount of epilation or by severity of radiation sickness. There were no unequivocal or clearcut parallel variations in the hemoglobin concentration or hematocrit reading, although minor variations were present.

2 By all three of the same standards, the depression of the lymphocyte count noted in table 2 appeared to be best defined for those who were most severely irradiated.

3 The elevation of the eosinophil count in irradiated persons, also brought out in table 2, likewise appeared best defined for the more heavily irradiated subjects (tables 7 through 10), although the data are not in complete agreement (tables 11 and 12). Whether this was a true effect of irradiation or merely reflected an increased incidence of parasitic infection in the heavily irradiated persons, due to lowered resistance and/or poorer food conditions, with increased infection at the time of the bombing, will be discussed further later in this report.

In the preceding section, it was noted that those subjects who had received the severest burns and trauma nevertheless appeared to show the highest erythrocyte counts. The results reported in this section would seem to indicate that those who received the greatest amount of irradiation had at the time of writing the lowest erythrocyte counts. One plausible hypothesis that would bring these two tendencies into a single pattern is that of those persons who were heavily irradiated and also received severe burns or other injuries many died. This would explain, among the epilated survivors who composed this series, a relative deficiency of those persons with both severe injuries and severe irradiation and a relative excess of those severely burned but not heavily irradiated, and/or those severely irradiated but without extensive burns or other injuries. It is felt that the present data are inadequate to serve as a basis for a rigorous test of this hypothesis.

COMMENT

It may safely be assumed that the majority of persons in this series reporting epilation in consequence of the atomic bombing exhibited within two months after the event a major depression in the number of formed elements of the peripheral blood¹. The studies herein reported reveal that two years after the bombing the peripheral blood manifested almost complete recovery from this insult to the hemopoietic system. However, there did appear to be a number of slight residua at the time of the study, of no apparent clinical significance but of definite statistical validity. In this section we shall attempt an evaluation of the meaning of these findings. First, however, as basic to any adequate discussion, the question of comparability of the control and the epilated populations on all scores except the irradiation factor must be considered.

The atomic bombing at Hiroshima produced sudden, widespread chaos. Casualties mounted to the tens of thousands, and in spite of valiant attempts, adequate care of the survivors was almost completely lacking. There was complete interruption of all normal economy for

a period of many weeks, and relief supplies failed to meet the demand in many instances. On the other hand, although Kure, the site of control observations, was subjected to bombings over a period of several months, the casualties were relatively few in number. Although there undoubtedly occurred disorganization of the normal economy, the degree and duration were minor in comparison with Hiroshima. Thus, the people were not subjected to the extreme privations encountered in Hiroshima. In the ensuing discussion, one question must constantly be kept in mind. Are the differences in the hematologic values observed in the two groups actually a residual effect of ionizing irradiation, or are they related to the associated unhygienic and innutritious aftermath? Also, it must be recognized that the surviving irradiated group were, within themselves, a selected group of the total population irradiated.

Erythrocyte Count—It was indicated in table 2 that the irradiated population of Hiroshima had a mean erythrocyte count slightly below that of the nonirradiated population of Kure, the difference amounting to 65,000 to 83,000 cells per cubic centimeter, or approximately 1.6 per cent of the Kure mean. There was a correspondingly slight reduction in hemoglobin concentration (the difference was 0.26 to 0.30 Gm per hundred cubic centimeters, or about 2.1 per cent of the Kure mean) and in hematocrit reading (0.48 per cent, about 1.2 per cent of the Kure mean). Since there were no significant differences relating to the cell constants, these differences were attributed to variations in the numbers of comparable cells rather than to qualitative effects on the erythrocytes. The important reservation relating to the spread of the distribution in Hiroshima will be discussed later in the paper.

The effect of ionizing irradiation on erythropoiesis has received considerable attention. The information in the literature on the results of long-continued irradiation and that on effects of repeated small doses of radiation is not strictly applicable in the interpretation of the data of this study. The literature on the erythrocytic response to acute exposures deals almost exclusively with the early picture²⁸ and indicates

28 (a) Minot, G. R., and Spurling, R. G. The Effect on the Blood of Irradiation, Especially Short Wave Length Roentgen-Ray Therapy, *Am J M Sc* **168** 215 (Aug.) 1924. (b) Shouse, S. S., Warren, S. L., and Whipple, G. H. Aplasia of Marrow and Fatal Intoxication in Dogs Produced by Roentgen Radiation of All Bones, *J Exper Med* **53**:421 (March) 1931. (c) Lawrence, J. H., and Lawrence, E. O. Biological Action of Neutron Rays, *Proc Nat Acad Sc* **22** 124 (Feb.) 1936. (d) Lawrence, J. H., and Tennant, R. Comparative Effects of Neutrons and X-Rays on the Whole Body, *J Exper Med*, **66** 667 (Dec.) 1937. (e) Aebersold, P. C., and Lawrence, J. H. The Physiological Effects of Neutron Rays, *Am Rev Physiol* **4** 25, 1942. (f) Warren, S., and Dunlap, C. E. Effects of Radiation on Normal Tissue. III. Effects

that there generally occurs a depression of erythropoiesis, with a resultant anemia within a few weeks, the severity of which is roughly related to the dose. The recovery from the anemia is relatively slow in comparison to the leukocytic recovery.²⁰ Stearner and others^{28k} administered 600 r of whole body radiation to rats and then followed the peripheral hematologic picture for a total of one hundred and sixty days. The lowest values for hemoglobin concentration and erythrocyte count were observed on the eighteenth day and were followed with a sharp recovery period. However, on the average, recovery did not appear to be complete at any time within the one hundred and sixty day period, although with the statistical measures employed, the differences between irradiated and control animals were not significant beyond the ninety-fourth day. The work of Jacobson and others^{28n, o} on the rabbit, although less conclusive statistically, tends to confirm the results of the work on the rat. Henshaw and others³⁰ observed relatively rapid recovery of the hematologic constituents in mice following single whole body exposures either to neutrons in doses up to 90 n or to gamma

of Radiation on the Blood and the Hemopoietic Tissues, Including the Spleen, the Thymus and the Lymph Nodes, Arch Path **34** 562 (Sept) 1942 (g) Beck, J S P, and Meissner, W A. Radiation Effects of the Atomic Bomb Among the Natives of Nagasaki, Kyushu, Am J Clin Path **16** 586 (Sept) 1946 (h) Craver, B N. Radioactive Emanations. Their Nature, Mechanism of Action, Biological Effects, and Tolerance Limits, J Indust Hyg & Toxicol **29** 196 (May) 1947 (i) Cantril, S T, Jacobson, L, and Nickson, J J. The Effects of Irradiation on the Blood and Blood Forming Tissues, MDDC 991, January 1943, declassified May 1946 (j) Bloom, W, and Jacobson L O. Some Hematologic Effects of Irradiation, Blood **3** 586 (May) 1948 (k) Stearner, S P, Simmons, E L, and Jacobson, L O. The Effects of Total Body X Irradiation on the Peripheral Blood and Blood Forming Tissues of the Rat, MDDC 1319, U S A E C (l) Suter, G M. Responses of Hematopoietic System to X-Rays, MDDC 824, declassified July 1947 (m) Howland, J W, and Warren, S L. The Effects of Irradiation from the Atomic Bomb on the Japanese, MDDC 1301, U S A E C (n) Jacobson, L O, and Marks, E K. Comparative Action of Cyclotron Fast Neutrons and X-Ray. II Hematological Effects Produced in the Rabbit by Fast Neutrons, MDDC 1372, U S A E C, June 1946, declassified Oct 1947 (o) Jacobson, L O, Marks, E K, Simmons, E L, Hagen, C W, and Zirkle, R E. Effects of X-Rays on Rabbits. II The Hematological Effects of Total Body X Irradiation in the Rabbit, MDDC 1174, July 1946, declassified July 1947

29 Warren and Dunlap^{28f} Cantril, Jacobson and Nickson²⁸ⁱ Bloom and Jacobson^{28j} Stearner, Simmons and Jacobson^{28k} Suter^{28l} Jacobson and Marks²⁸ⁿ

30 Henshaw, P S, Snider, R S, Riley, E F, Stapleton, G E, and Sinkle, R E. Comparative Late Effects of Single Doses of Fission Neutrons and of Gamma Rays, MDDC 1254, June 1946, declassified August 1947

rays in doses up to 700 r, the only significant late hematologic finding noted was the development of lymphomas

On the other hand, the Japanese diet had for at least the five years previous to the study been deficient in many respects a factor which did not favor adequate blood formation²⁷ From recent surveys, the composition of the average Japanese diet during that period can be estimated to have consisted of 60 Gm of protein, 12 Gm of fat and 400 Gm of carbohydrate however, only about one tenth of the protein intake was of animal origin⁷ It has been stated that meat eaters average a higher number of red cells than vegetarians³¹ Whipple and Robscheit-Robbins³² have extensively investigated the effects of various nutrients on blood regeneration Evidence indicates then, that diet is an extremely important consideration, and that in a population which originally had an inadequate base line standard the further innutritious circumstances created by the atomic bombing could conceivably have resulted in such hematologic differences as are indicated here Even the fact that erythrocyte values appeared to be most depressed in those persons who received the greatest amount of radiation may only indicate that these persons suffered the greatest material loss and so, economically, fared particularly badly with consequent poor nutrition The factors of irradiation and innutritious conditions perhaps were in effect, additive

Leukocyte Count—There was found to be no significant difference between mean leukocyte counts for the irradiated and nonirradiated groups but there was a slight depression of relative lymphocyte count, amounting to 1.39 to 2.02 per cent, and a slight elevation of relative eosinophil count, amounting to 0.99 to 1.83 per cent The general increase in mean leukocyte count, in both epilated and control series, was probably an expression of the frequent infections observed which were minor but which did not eliminate persons from the series

31 Wintrobe, M. M. The Erythrocyte in Man, *Medicine* **10** 195 (May) 1930

32 Whipple, G. H., and Robscheit-Robbins, G. S. Blood Regeneration in Severe Anemia. Standard Basal Ration Bread and Experimental Methods, *Am J Physiol* **72** 395 (May) 1925, Favorable Influence of Liver, Heart, and Skeletal Muscle in Diet, *ibid* **72** 408 (May) 1925, Iron Reaction Favorable Arsenic and Germanium Dioxide Almost Inert, *ibid* **72** 419 (May) 1925, Green Vegetable Feeding, *ibid* **72** 431 (May) 1925, Influence of Striated and Smooth Muscle Feeding, *ibid* **79** 260 (Jan) 1927, Influence of Kidney, Chicken and Fish Livers, and Whole Fish, *ibid* **79** 271 (Jan) 1927, Influence of Dairy Products on Hemoglobin Production, *ibid* **79** 280 (Jan) 1927. Whipple, G. H. Hemoglobin Regeneration as Influenced by Diet and Other Factors, *J A M A* **104** 791 (March 9) 1935. Protein Production and Exchange in the Body Including Hemoglobin, Plasma Protein and Cell Protein, *Am J M Sc* **196** 609 (Nov) 1938

The extreme sensitivity of the lymphocyte to acute ionizing irradiation has been appreciated for many decades,³³ but recovery has been said to be adequate within a relatively short time^{28f} It has been recently reported, however, that in the rabbit, the lymphocyte count was depressed for a period of ninety days after acute exposure to 800 r^{28j} Other investigators have reported that in the case of rats exposed to large single doses of whole body radiation, a possible discernible effect was observable in the lymphopoietic tissue as long as thirty-five days later, even though recovery, as indicated by the state of the peripheral blood, was essentially complete at thirty days^{28k}

Our data do suggest that there possibly existed greater residual depression of the lymphocyte count in those persons who received the heavier doses of radiation, but likewise they may indicate that it was these groups which showed the greatest increase in percentage of eosinophils Eosinophilia is of recognized occurrence during the recovery phase in acute exposure to ionizing irradiation in as much as 10 to 20 per cent of cases^{28a, f} However, for the most part, eosinophilia is related to chronic or repeated exposure³⁴ The duration of eosinophilia following acute exposure has received little attention The high incidence of parasitic infection undoubtedly accounts for the rather high values observed in the controls,³⁵ but whether the relatively higher values in the Hiroshima subjects were an expression of increased parasitic disease cannot be stated without further study The unhygienic conditions so prevalent in Hiroshima for several months after the bombing certainly would have favored transmission and increased morbidity If this was the causal relation, the depression of the lymphocyte count was perhaps only a compensatory depression, in view of the similar mean leukocyte counts An increased incidence of parasitic infection in Hiroshima may, of course, be a partial explanation of the difference in erythrocyte counts

33 Minot and Spurling^{28a} Heineke, H Ueber die Einwirkung der Roentgenstrahlen auf Tiere, *Munchen med Wchnschr* **50** 2090, 1903

34 Minot and Spurling^{28a} Martland, H S Occupational Poisoning in Manufacture of Luminous Watch Dials General Review of Hazard Caused by Ingestion of Luminous Paint, with Special Reference to the New Jersey Cases, *J A M A* **92** 466 (Feb 9), 552 (Feb 16) 1929, The Occurrence of Malignancy in Radioactive Persons, *Am J Cancer* **15** 2435 (Oct) 1931

35 (a) Duff⁶ (b) Weech, A A, Goettsch, E, and Reeves, E B Nutritional Edema in the Dog I Development of Hypoproteinemia on a Diet Deficient in Protein, *J Exper Med* **61** 299 (March) 1935

Plasma Protein Values—The plasma protein values in Hiroshima were slightly elevated over those in Kure. Whether this was on a basis of nutrition or of irradiation cannot be decided at the present time. To the extent that plasma protein levels could be taken as a criterion for gross malnutrition,^{85b} there was no evidence of the possible greater impairment of nutrition in Hiroshima discussed previously. The high levels of plasma protein observed in both cities are noteworthy. Similar high levels were observed by the Joint Commission, using the copper sulfate method, in 1945.¹ The determination of plasma protein values by the copper sulfate gravity method depended on certain constants, derived from a study of American subjects. The necessary studies to determine whether the extrapolation to Japanese subjects was a valid procedure have not been carried out at the time of writing. It is possible that the character of the Japanese diet was reflected in the constituents of the blood to the point where a given value for specific gravity did not have the same significance for the two groups.²⁷

Variation—Perhaps one of the more significant statistical findings to emerge from this study is the greater variability of individual hematologic values in the irradiated group in comparison with those of the control group. In the case of determinations concerned with the erythroid elements, this greater variability seems to be due chiefly to the fact that counts for a certain fraction of the population, for reasons not entirely evident, had failed to return to normal levels, with a resultant increased spread in the distribution of individual determinations. That considerable qualitative and quantitative variability of hematologic recovery after irradiation exists within various animal species is a well recognized fact.³⁶ For leukocyte determinations in which the mean total counts are similar, the explanation is more obscure.

The fact that the standard deviations recorded for the control population are considerably greater than those commonly accepted may lead some to question the validity of conclusions concerning relative variability. Throughout this investigation, we have been particularly conscious of procedural errors. We have attempted to evaluate the limitations of the various hematologic methods by as precise an estimation as possible of the errors involved in the determination of each value. These attempts have indicated that there was a substantial error due to inherent deficiencies of the methods, and also to personal inter-

36 Warren and Dunlap^{28f} Bloom and Jacobson^{28j} Stearner, Simmons and Jacobson^{28k}

pretations of the "end point" The reflection of these errors in the values for cell constants has been pointed out in some detail On the basis of certain statistical considerations, the expected ranges of the constants for 95 per cent of values have been found to be considerably larger than those generally accepted as describing the range of normal values For instance, Wintrobe¹⁶ stated that 98 per cent of normal determinations of mean cell volume would fall within ± 80 cubic microns of the mean, 87.0 cubic microns Ninety-eight per cent of the frequencies represent ± 2.7 standard deviations, therefore, 1 standard deviation is $\frac{\pm 80}{2.7}$, or approximately ± 30 cubic microns We have indicated, on the basis of calculations utilizing certain estimates of the variability of the hematocrit reading and the erythrocyte count and their correlation coefficient, that the standard deviation of the mean cell volume should approximate at least ± 5.2 cubic microns The range for 98 per cent of values would then be $2.7 \times (\pm 5.2)$ or ± 14.0 cubic microns But even if one accepts the fact that the values customarily accepted as representing the range of the constants are too narrow, it must be admitted that in the control samples of both Japanese and American subjects, the observed variation in the mean cell volume was significantly greater than the calculated expectation At least three factors which may have contributed to the greater variability of this and other determinations can be recognized (1) In calculating the statistical expectation, extremely conservative estimates of population variability were utilized, (2) this study involved a decidedly more heterogeneous control population than was the case in the studies of Americans, designed to determine the normal range of the blood constants, and (3) noncertified equipment was used The further possibility of technicians' errors must be recognized But whereas all these factors may have contributed to a greater real and apparent variability in the "normal" population used in this study than in other normal populations, they cannot be utilized to explain the differences between Kure and Hiroshima, since the two laboratories were operated under comparable conditions, with the same staff

SUMMARY

An attempt has been made to answer the following question What was the peripheral hematologic picture twenty to thirty-three months after the atomic bombing of Hiroshima, in persons who received relatively large amounts of whole body radiation?

The criterion adopted for the selection of relatively heavily irradiated subjects was the occurrence of scalp epilation. Epilated subjects were selected at random, through the use of a questionnaire. The majority were school children.

A control population comparable in age, sex, nutritional status and occupation was studied in the city of Kure, which is located some 18 miles (28.97 kilometers) from Hiroshima.

In Hiroshima, 924 subjects were examined, in Kure, 935.

Each person selected for study completed a brief history and was given a brief physical examination, as many of the following blood values as circumstances permitted were then determined: erythrocyte and leukocyte counts, differential blood count, hemoglobin concentration, hematocrit reading, plasma protein level and, for a smaller number of persons, reticulocyte count.

A detailed evaluation of the errors involved in the standard blood studies is presented as a basis for an appreciation of the significance of these findings.

Results are compared not only in terms of the mean values for the two populations but also in terms of the mean differences between randomly established pairs of similar control and epilated individual subjects.

The irradiated subjects of this study appeared for the most part to have made a complete recovery from the depression of the peripheral blood values which may be assumed to have followed the bombing. However, various significant differences between the two populations were observed.

- 1 Erythrocyte count, hemoglobin concentration and hematocrit reading were slightly, but significantly, depressed for the subjects in Hiroshima.

- 2 Although the total leukocyte count was the same in the two cities, in Hiroshima there were a slight relative depression of lymphocytes and a slight elevation of eosinophils.

- 3 Plasma protein values were possibly slightly higher in Hiroshima.

- 4 There was significantly greater variability in the observations made in Hiroshima than in those made in Kure.

These differences cannot be attributed to a differential response on the part of any particular age or sex group.

Epilated persons who experienced associated flash burns or trauma showed mean erythrocyte values which were higher, if anything, than the values for those who did not suffer such associated injury, from

which it is inferred that the greater frequency of these injuries in Hiroshima than in Kure does not account for the hematologic differences between the groups

Those individual subjects who, by any of a number of criteria, absorbed greater amounts of radiation tended to show the most pronounced depression in erythrocyte and lymphocyte counts and the greatest elevation in eosinophil counts

It is felt that in view of the great medical and civil disruption in Hiroshima after the bombing, caution must be exercised in attributing the slight recorded differences to the atomic bombing, although it seems possible that irradiation was, to some extent, responsible

CLINICAL SIGNIFICANCE OF BACTEROIDES

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CERTAIN anaerobic, nonsporing, gram-negative bacilli are classified in the genus *Bacteroides*¹ (Excluded from this designation are the genera *Dialister* and *Fusiformis*, the former being characterized by small size and the latter by pointed ends) These organisms are saprophytic inhabitants of the intestine, the urinary tract, the pharynx and the female genital tract² Comparatively few studies of infections induced by *Bacteroides* have been reported in this country The impression prevails, therefore, that it is a rare, even exotic, cause of human disease This report is concerned with the clinical importance of *Bacteroides* in a group of cases in which this organism was recovered

Dack's comprehensive survey³ may be consulted for a review of the morphology, taxonomy, biochemical reactions and antigenic characteristics of *Bacteroides* "Bergey's Manual of Determinative Bacteriology"¹ presents a detailed, but provisional, classification of this group of bacteria A number of provocative studies purporting to demonstrate the evolution of variant L type colonies from *Bacteroides* have been reported by Dienes and his collaborators⁴

METHODS

The routine technics of anaerobic cultivation used in our laboratory were adequate for the isolation of *Bacteroides* An anaerobe jar such as that described by Brewer,⁵ was utilized Employment of a catalyst was found to be superfluous when a high degree of suction could be attained

From the Department of Medicine, Stanford University School of Medicine

1 Breed, R S, and others Bergey's Manual of Determinative Bacteriology, ed 6, Baltimore, Williams & Wilkins Company, 1948

2 Lemierre, A On Certain Clinical Forms of Septicemia with "Funduliformis" Bacillus, in Hamburger, J Recherches médicales en France pendant la guerre 1939-1945, Paris, Ernest Flammarion, 1947, p 7

3 Dack, G M Non-Sporeforming Anerobic Bacteria of Medical Importance, Bact Rev 4 227, 1940

4 (a) Dienes, L, and Smith, W E The Significance of Pleomorphism in *Bacteroides* Strain, J Bact 48 125, 1944 (b) Dienes, L The Isolation of L Type Cultures from *Bacteroides* with the Aid of Penicillin and Their Reversion into the Usual Bacilli, ibid 56 445, 1948

5 Brewer, J H A Modification of the Brown Anaerobe Jar, J Lab & Clin Med 24:1190, 1939

and when carbon dioxide and hydrogen were pumped into the jar in succession after the evacuation of air. None of the anaerobic methods of blood culture⁶ were utilized. Routine methods of blood culture, suitable for the isolation of most aerobic and anaerobic bacteria, were used.

No attempt to identify individual species was made in this laboratory. The classification of *Bacteroides* has been simplified in recent years, at

TABLE 1—*Sites from Which Bacteroides Was Isolated in 47 Cases*

Source	Number of Cases	Total Number of Cases
Blood		2
Cerebrospinal fluid		1
Thyroid gland		1
Abdomen		3
Intra abdominal abscess	1	
Retropertitoneal abscess	1	
Rectal abscess (carcinoma)	1	
Lungs		5
Empyema	2	
Lung abscess	1	
Bronchiectasis	1	
Postpneumonectomy bronchial fistula	1	
Osteomyelitis		2
Otolaryngologic area		2
Maxillary sinus (right)	1	
Auditory canal (right)	1	
Urinary tract		4
Superficial lesions		12
Scalp abscesses	1	
Deltoid abscess (left)	1	
Hidradenitis suppurativa	1	
Pararectal abscess	2	
Inguinal abscess	2	
Breast abscess	1	
Sebaceous cyst abscess above right ear	1	
Inflammation of parotid gland	1	
Abscess of pilonidal cyst	1	
Pyodermic ulcer of leg	1	
Female genital tract		8
Tubo ovarian abscess	3	
Cul de sac abscess	1	
Bartholinian abscess	1	
Paraurethral abscess	1	
Vaginal abscess	1	
Vulval ulcer	1	
Uterine culture		7
Totals	30	47

present, *Bacteroides funduliformis* and *Bacteroides fragilis* appear to be the principal species clinically recognized. The former is distinguished from the latter by its pleomorphism and its supposedly greater invasiveness.⁶ However, the differences in the clinical manifestations of infection with the two species are relatively minor.⁷ Dienes^{4b} stated that any classification was unnecessary, implying that diversities in strains account for the assumed distinctions in species.

6 (a) Smith, W. E., and Ropes, M. W. *Bacteroides Infections*, New England J. Med. **232** 31, 1945. (b) Pham, H. C. *Les septicémies dues au Bacillus funduliformis*, Thesis, Paris, 1935.

7 Ternois. *Les septicémies a Bacillus fragilis*, Ann. de med. **44** 201, 1938.

INCIDENCE

Bacteroides was recovered in the cases of 47 patients admitted to the Stanford University Hospital clinics in the eight year period from 1940 to 1948. The incidence of *Bacteroides* according to the source and the age and sex of the patients is compiled in tables 1, 2 and 3. *Bacteroides*, according to the data in table 1, is a ubiquitous organism. The female genital tract and various superficial areas of the body were the most common sources. *Bacteroides* was encountered most frequently in the cases of young adults, although all age groups were well represented. Infections of females were predominant in this series even when the female genital tract was excluded as a source.

TABLE 2—*Incidence of Bacteroides According to Age of Patients*

Age, Years	Number of Patients	Percentage
1 to 15	6	12.8
16 to 30	19	40.4
31 to 45	12	25.5
46 to 60	6	12.8
61 and over	4	8.5
Totals	47	100.0

TABLE 3—*Incidence of Bacteroides According to Sex of Patients*

	Male Patients		Female Patients	
	Number	Percentage	Number	Percentage
Incidence in all cases	14	30.0	33	70.0
Incidence in all cases excluding infections of genital tract	14	42.4	19	57.6

CLINICAL FINDINGS

Bacteriemias—The primary foci of *Bacteroides* septicemia and bacteremia include tonsillar and peritonsillar abscesses, similar lesions of the mouth and jaw, otitis media, purulent endometritis, infection of the urinary tract and intestinal abscesses.⁸ Many of the reported *Bacteroides* septicemias might more accurately be designated as sepsis with bacteremia. These septicemias and bacteremias are usually morbid processes with a high mortality rate.⁹ Arthritis, icterus, pulmonary emboli and

8 Lemierre, A. (a)², (b) On Certain Septicæmias Due to Anaerobic Organisms, *Lancet* 1 701, 1936

9 (a) Pham^{6b} (b) Lemierre, A., Reilly, J., and Laporte, A. Les septico-pyohémies à *Bacillus funduliformis*, *Ann de med* 44 165, 1938

and chill occurred. Three days afterward, on December 24, the patient was admitted to the hospital. While the patient was being examined late that day, a deep stupor developed precipitously.

The temperature was 37.8 C (100.0 F), the pulse rate 110, the respiration rate 30 and the blood pressure 130 systolic and 80 diastolic. Rales were heard over the right lung field and at the base of the left lung. Slight cardiac enlargement but no murmurs or arrhythmias were noted. There was a massive ventral hernia, and generalized pelvic tenderness was present.

The white blood cell count was 14,800 per cubic millimeter of blood. There was a marked predominance of neutrophils, nonfilamentous forms being very numerous. The hemoglobin concentration was 11.3 Gm per cubic centimeter of blood. Slight proteinuria was noted. Elevated blood urea values (61 and 56.8 mg per cent) were recorded early in the course. The icterus index, tests repeated twice, was 7.5. The plasma protein level was 7.5 Gm per hundred cubic centimeters.

A nonhemolytic streptococcus was isolated from blood obtained one day after entry. This organism was inhibited with 0.1 unit of penicillin per cubic centimeter of blood. One day later, gram-negative bacilli of the paracolon group and *Clostridium welchii* were observed in the bloodstream. The latter was inhibited with 0.1 unit of penicillin per cubic centimeter. *Bacteroides* was the lone organism recovered from the blood on three successive occasions; it was resistant to 0.4 unit of penicillin per cubic centimeter. These positive blood cultures were made on the fourth, fifth and seventh days of hospitalization. Two subsequent blood cultures gave negative results. Coliform bacilli were isolated from the urine on the fifth day of hospitalization.

Atrial fibrillation developed one day after the patient was admitted. Immediate digitalization was followed by a reversion to sinus rhythm in two days. Maintenance doses of digitoxin were continued. Three hundred and twenty thousand units of penicillin were administered daily. Sulfadiazine (2 to 4 Gm daily) was given, starting on the eighth day of hospitalization. Transfusions of whole blood and parenteral hydration constituted supportive therapy.

The spontaneous drainage of sanguinous, purulent material from the vagina occurred ten days after admission. A rectovaginal fistula originating from an abscess located in the distal end of the bowel was revealed to be the basis of the discharge.

On the tenth and eleventh days of hospitalization, certain of the organisms previously found in the blood stream, including aerobic gram-negative bacilli, *C. welchii* and *Bacteroides*, were isolated from the vaginal discharge. Coliform bacilli and penicillin-resistant nonhemolytic streptococci (organisms not previously recovered from the blood) were also obtained from the vaginal discharge.

The principal diagnoses were rectal fistula due to lymphogranuloma venereum, pelvic abscess, rectovaginal fistula, bacteremia, arteriosclerotic heart disease and bronchopneumonia.

An extremely febrile course, including recurrent chills and severe prostration, persisted for two weeks. The temperature fluctuated greatly, reaching a height of 40.6 C (105.1 F) on one occasion.

The leukocytosis persisted for about three weeks, the count attaining a height of 38,400 about two weeks after the patient's entry. Anemia developed, the hemoglobin concentration falling to 8.6 Gm and the red blood cell count to 2,800,000 by the sixteenth day of hospitalization. Improvement commenced shortly afterward, and the trend was one of progress despite recurrent chills and

fever, signs of pulmonary edema, transient dependent edema, an episode of non-descript precordial pain and hypertension The patient was dismissed thirty-five days after her entry

Bacteroides was the predominant, although not the initial, invader of the blood stream The resistance of the organism to penicillin was reflected in the delayed response to therapy It was apparent that the abscess of the bowel and the resultant rectovaginal fistula constituted the primary source of the bacteremia Thrombophlebitis, arthritis and icterus, commonly present in invasion of the

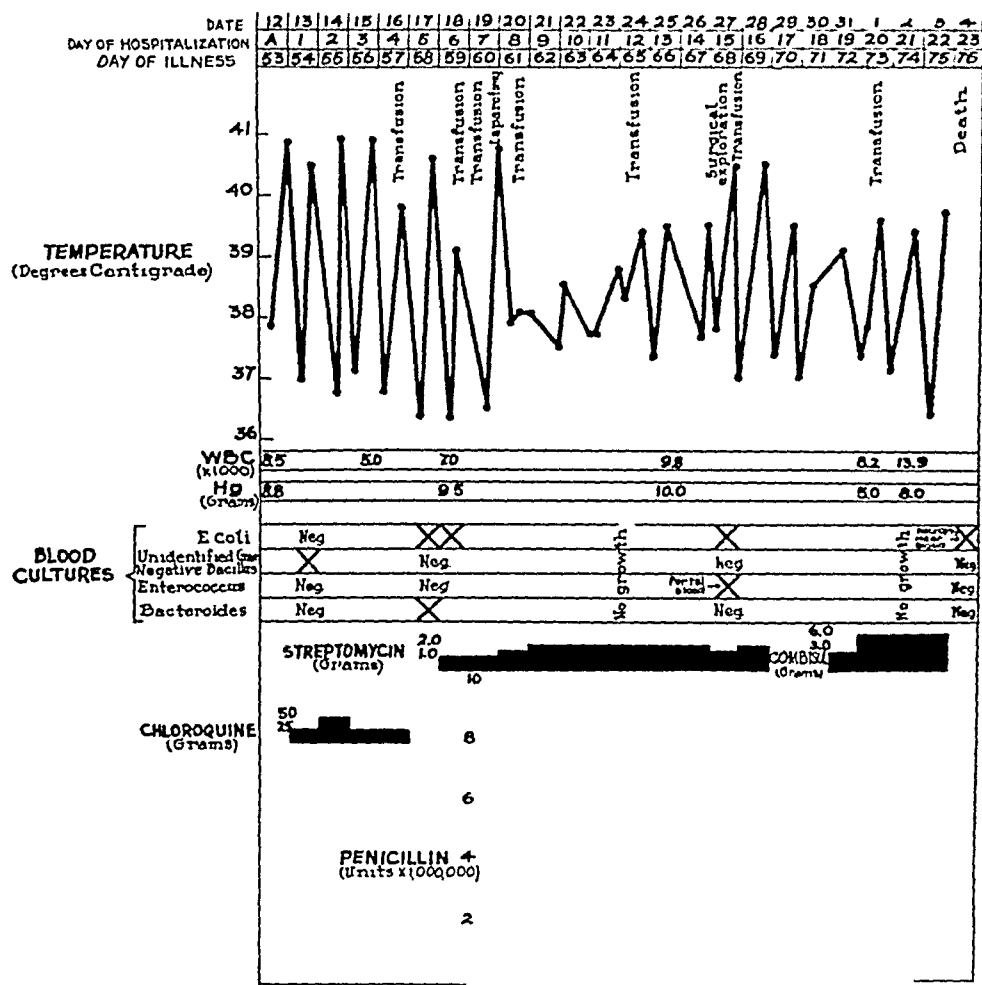


Chart 2—Course in bacteremia (case 2) Combisul® contains equal parts of sulfadiazine, sulfathiazole and sulfamerazine

blood stream by Bacteroides, were conspicuously absent from this case The frequent resemblance of Bacteroides sepsis with bacteremia to that caused by other pyogenic organisms has been stressed¹²

CASE 2—A white housewife of 39 (chart 2) had been in good health until March 21, 1948, when colicky lower abdominal pain, nausea, vomiting and diarrhea began, followed in two days by temperatures to 104 F Chills and fever

12 Teissier, P , Reilly, J , Rivalier, E, and Stefanescu, V Les septicemies primitives dues au Bacillus funduliformis, Ann de med 30 97, 1931

recurred daily, but the abdominal distress subsided after the third week of illness. About 1,000,000 units of penicillin had been administered without effect just prior to the patient's entry to the Stanford University Hospital on May 12.

The temperature was 37.8 C (100.0 F), the pulse rate was 100, and the blood pressure was 120 systolic and 75 diastolic. The patient was sallow and listless. A soft, systolic murmur along the left sternal border, tenderness in the right upper quadrant of the abdomen and a palpable spleen extending 4 finger-breadths below the left costal margin were the only contributory observations at that time.

A leukocyte count of 18,600 had supposedly been observed nine days prior to entry. On admission, the white blood cell count was 8,640 with 79 per cent neutrophils. Pronounced anemia was present at the time of entry and became intensified, despite blood transfusions, with a decline to a hemoglobin concentration of 5.0 Gm and a red blood cell count of 1,960,000 two days before the patient's death. The corrected sedimentation rate on entry was 67 mm per hour. Early in the course, the direct bilirubin value was 1.4 mg per hundred cubic centimeters and the indirect bilirubin value, 3.2 mg, the reaction for urinary urobilinogen was positive in a dilution of 1:160, and the icterus index was elevated to 20. The icterus index subsequently declined, a value of 7.5 being recorded four days prior to the patient's death.

A variety of organisms were found in the blood, including a pigment-forming gram-negative bacillus, *Bacteroides*, *Escherichia coli* and, from the portal blood, enterococci. On the 3 occasions that *Esch. coli* were recovered prior to the patient's death, 5 to 10 micrograms of streptomycin per cubic centimeter were sufficient for complete inhibition. Conversely, the single specimen of *Bacteroides* isolated early in the course of the illness was resistant to 50 micrograms of streptomycin per cubic centimeter and to 6 units of penicillin per cubic centimeter. (Cultures made at autopsy of the appendical abscess and of heart blood revealed *Esch. coli* resistant to 60 micrograms of streptomycin per cubic centimeter.)

The fever, chills and lethargy continued. A progressive increase in the extent of splenic enlargement was noted. A laparotomy performed on the seventh day of hospitalization and a right posterior flank approach on the fifteenth day revealed no disease. Nineteen grams of streptomycin and 40,000,000 units of penicillin were administered within two weeks without effect. Chloroquine, given early for suspected malaria, digitalis and more than 20 Gm of sulfonamide drugs were similarly ineffectual.

Signs of fluid at the bases of both lungs had developed by the twelfth day. Roentgenographic studies at that time revealed a frank pleural effusion on the right side. Pronounced dependent edema appeared on the fifteenth day of hospitalization but diminished in four days. The tachycardia increased, the rate rising to 130, there was a pronounced gallop rhythm. Protein, coarsely granular casts and white blood cells were observed in the urine fifteen days after admission. Meanwhile, swinging of the temperature, severe shaking chills and lethargy continued. The peritoneal fluid, cultured about one week prior to the patient's death, revealed numerous enterococci plus a few *Esch. coli* and a few hemolytic streptococci. A culture of the wound performed one day later showed a heavy growth of *Esch. coli*. Severe respiratory distress supervened twenty-three days after entry, and the patient died. A definite diagnosis was not made before death.

An autopsy revealed acute purulent appendicitis, acute purulent pyelophlebitis, multiple hepatic abscesses and chronic local peritonitis. It is believed that a

localized abscess formed at the site of the appendical adhesion to the pelvic portion of the peritoneum. Acute purulent involvement of the portal vein followed with ensuing multiple abscesses of the liver.

It is evident that *Esch coli* was the principal cause of the septic process. The importance of the subordinate role performed by *Bacteroides* is difficult to evaluate. At a period when blood-borne *Esch coli* were definitely sensitive to streptomycin, the single culture of *Bacteroides* was refractory to the antibiotic therapy then in progress. It should be noted further that a heavy growth of *Esch coli* may readily mask the presence of *Bacteroides*, particularly inasmuch as an obligate anaerobic bacterium is considerably more fastidious about its environmental requisites than is *Esch coli*. *Bacteroides* has been described as a frequent cause of appendicitis¹³. Hepatic abscesses and bacteremias have been known to arise from *Bacteroides appendicitis*¹⁴.

Meningitis—Smith and his associates,¹⁵ in 1944, reviewed 14 cases of *Bacteroides* infection of the central nervous system, 4 of them being their own. Meningitis was diagnosed in 12 instances. Chronic otitis media was the common origin of such infection, and invasion of the mastoid was rather common. *Bacteroides meningitis* was characterized by the acute onset of fever, headache, and stiffness of the neck. The spinal fluid has been found to be cloudy, with an elevated cell count, increased protein content and decreased sugar content. The prognosis was hopeless prior to the advent of chemotherapy and proper supportive therapy. Three of the 4 patients whose cases were described by Smith and others and a patient in another recent case of *Bacteroides meningitis*¹⁶ recovered from the disease. Sulfonamide therapy and proper surgical and supportive therapy were important factors in the cases with a favorable outcome.

CASE 3—A Negro of 21 (chart 3) had had a mass located at the angle of the jaw on the right side since the age of 2. The mass had enlarged despite surgical excision and radiation therapy. Roentgenograms made in October had revealed chronic, bilateral mastoiditis. The patient entered the hospital on December 14, 1947, diagnoses of mixed tumor and, later, adenocarcinoma of the parotid gland were made.

The area around the right ear was extremely firm, the right ear protruded, the right external auditory canal was occluded by blood and pus and sound was lateralized to the right in the Weber test. The mouth could be opened only 2 cm. Paralysis of the right facial nerve was present.

13 Veillon, A., and Zuber, A. (a) Sur quelques microbes strictement anaerobies et leur role dans la pathologie humaine, *Compt rend Soc de biol* 4 253, 1897, (b) Recherches sur quelques microbes strictement anaerobies et leur rôle en pathologie, *Arch de med exper et d'anat path* 10:517, 1898.

14 Lemierre^{8b} Lemierre, A., and Reilly, J. Roles des microbes anaerobies dans l'etiologie des septicopyohemies consécutives aux appendicites, *Presse med* 53 105, 1945.

15 Smith, W. D., McCall, R. E., and Blake, T. J. *Bacteroides* Infections of the Central Nervous System, *Ann Int Med* 20 920, 1944.

16 Ballenger, J. J., Schall, L. A., and Smith, W. E. *Bacteroides Meningitis* Report of a Case with Recovery, *Ann Otol, Rhin & Laryng* 52 895, 1943.

Radical dissection of the right ear and the surrounding tissue was performed four days after the patient's entry. A hard, 10 by 5 cm mass was found to be attached to tissue behind the right ear. This was excised, as was much of the ramus of the mandible and the first inch of the zygomatic process. A cerebrospinal leak occurred at the base of the skull during the operation. The patient's recovery from the operations was complicated by a severe hemorrhage and fever. Penicillin and streptomycin were administered and the right common carotid artery and internal jugular vein were ligated and divided on Jan 1, 1948. A skin graft

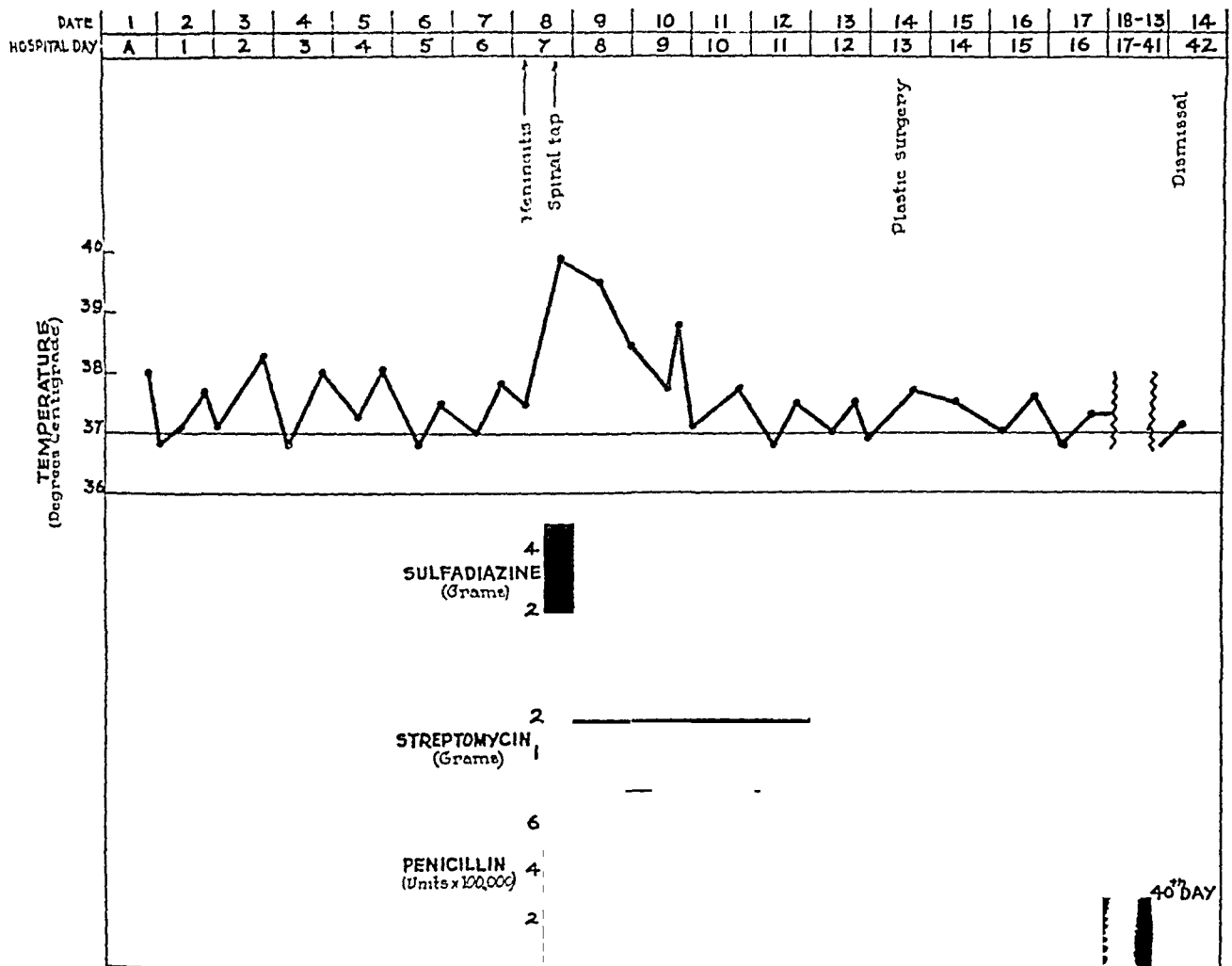


Chart 3—Course in meningitis (case 3)

was applied on January 14. The white blood cell count was 11,150 on January 16.

The patient reentered the hospital on February 1 because of an infection involving the area from which skin had been obtained on the right posterior thigh. Drowsiness, irrationality, frontal headache and a temperature of 39.8°C (103.6°F) suddenly developed eight days later. Tenderness, pain and stiffness of the neck were present. A lumbar puncture revealed a high protein content and the presence of large numbers of polymorphonuclear leukocytes and of *Bacteroides* in pure culture in the spinal fluid. The white blood cell count was 8,920, the hemoglobin concentration was 12.5 Gm, and the red blood cell count was 4,400,000. Penicillin, streptomycin and sulfadiazine were promptly administered.

There was no nuchal stiffness or tenderness by the following day, and the temperature had declined to 38.5 C (101.3 F). Recovery was so rapid that another skin graft was undertaken on February 14. The patient left the hospital on March 14. There were no complaints or evidence of recurrence, either of meningitis or of the neoplasm, on November 16.

The sudden onset of fever, headache, irrationality and stiffness of the neck, and equally rapid recovery (probably in response to the simultaneous administration of sulfadiazine, streptomycin and penicillin) characterized this case of *Bacteroides* meningitis. The relative efficacy of the three therapeutic agents is difficult to evaluate. A successful outcome in other cases has been attributed, in part at least, to sulfonamide therapy. However, the extremely rapid response of this patient to treatment indicates only that one or the other of the antibiotic drugs, and possibly both, contributed to the favorable result.

The evidence of otitic infection on the entry of the patient and the history of mastoiditis diagnosed by roentgenographic examination provided a suitable background for the probable origin of the disease. One may surmise that the preceding major operation on the area of the right ear and the attendant stormy course were important contributory factors in the pathogenesis of the meningitis.

Involvement of the Thyroid Gland—There has been casual mention of thyroiditis occurring in the course of *Bacteroides* septicemia.⁸

CASE 4—One patient in the series, a white man of 64, harbored *Bacteroides* in the thyroid gland. Moderate enlargement of the thyroid gland had been present for twenty to twenty-five years. The patient entered the hospital because sudden enlargement and tenderness of the thyroid gland associated with dysphagia had occurred four days before. Fever, mild leukocytosis and moderate anemia were present. The mass in the neck, weighing 308 Gm., was removed by a subtotal thyroidectomy, the temperature then rapidly declined to normal. The patient was discharged thirty-four days after entry. The surgical and pathologic reports concurred in a diagnosis of thyroid adenomas plus hemorrhages, both old and recent, into the thyroid gland and thyroiditis. A microscopic examination disclosed areas of leukocytic infiltration and necrosis.

Sanguinous material aspirated from the enlarged thyroid gland thirteen days after the patient's entry revealed *Bacteroides* in pure culture. Similar organisms were recovered from the thyroid gland at the time of the operation nine days later. Three blood cultures, taken on the tenth, thirteenth and fourteenth days of hospitalization, respectively, were sterile.

It is believed that this is the first report in the United States of the isolation of *Bacteroides* from the thyroid gland.

Abdominal Lesions—*Bacteroides* has been found in cases of appendicitis,¹³ peritonitis^{6a} and infected carcinoma of the large intestine.¹⁷ Only 1 of 5 patients with *Bacteroides* peritonitis without bacteremia died, whereas 5 of 6 instances of *Bacteroides* septicemia arising from infection in carcinoma of the bowel were fatal. Smith and Ropes^{6a} pointed

¹⁷ Dixon, C. F., and Deuterman, J. L. Postoperative *Bacteroides* Infection. Report of Six Cases, *J. A. M. A.* **108**: 181 (Jan. 16) 1937.

out the probable frequency of intra-abdominal infections due to *Bacteroides*, leakage of the contents of the bowel was the postulated route of invasion

CASE 5—A white man of 28 (chart 4) had had pain in the right lower quadrant of the abdomen, diagnosed as due to appendicitis, about six weeks prior to his entry to the hospital. An appendectomy had been performed, and there was apparent recovery within eleven days. The first attack of pain in the right upper quadrant occurred about two weeks later. This quickly subsided but was

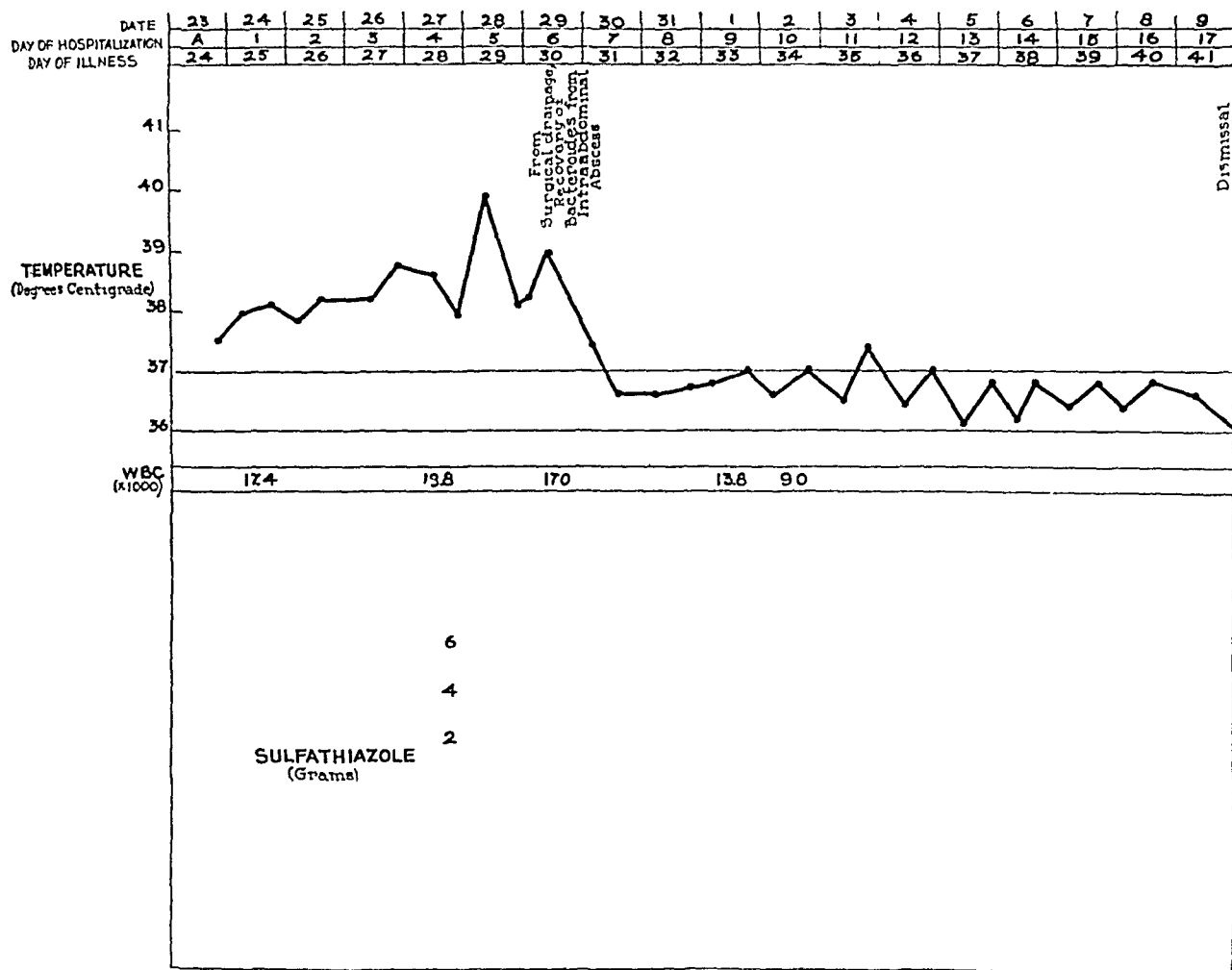


Chart 4—Course in case 5 (intra-abdominal abscess)

followed in a week by a severe exacerbation of similar pain plus a temperature of 101 F, nausea and vomiting, and possible blood in the stools. After four days, the attack subsided. On the patient's entry, aside from a temperature of 37.7 C (99.9 F), the only contributory findings were tenderness and spasm in the right upper quadrant.

The white blood cell count varied between 15,000 and 18,000 and returned to normal after surgical intervention. The icterus index and the value for the van den Bergh test were within normal limits. *Bacteroides* was isolated in pure culture from material obtained from the intra-abdominal abscess at the operation.

Roentgen studies, performed one day after admission, were inconclusive aside from failure to visualize the gallbladder. The fever and tenderness of the right upper quadrant persisted until the sixth day of hospitalization. At that time, a laparotomy revealed an intra-abdominal abscess, which was immediately incised and drained. Omental adhesions were observed on the lateral and posterior surfaces of the gallbladder, the extrusion of 2 or 3 ounces (57 to 85 Gm) of thick, yellow pus occurring on digital probing of the involved area. The liver was normal in appearance. Despite considerable foul, serous drainage, the subsequent course was characterized by rapid improvement and the patient was dismissed from the hospital seventeen days after admission.

It may be significant that appendicitis preceded the occurrence of the intra-abdominal abscess in case 5. *Bacteroides*, the lone etiologic agent discovered in this instance, has been described as an appendical inhabitant¹³. The relatively benign course in this case corresponded with the usual favorable outcome of *Bacteroides* peritonitis.^{6a}

Bacteroides was recovered from abscesses secondary to malignant neoplasms in 2 additional cases.

CASE 6—A woman of 22 had a retroperitoneal sarcoma. *Bacteroides* and *Bacillus subtilis* were present in a large abscess adjacent to the neoplasm. The *Bacteroides* was penicillin sensitive. The patient's early death did not seem related to the abscess, the highly malignant sarcoma accounting for the rapid downhill course.

CASE 7—*Bacteroides* and anaerobic nonhemolytic streptococci were recovered from an abscess adjacent to an inoperable rectal carcinoma. The absence of severe symptoms, aside from a rectal hemorrhage readily ascribed to the neoplasm, indicated that the abscess was not of great clinical importance.

Osteomyelitis—Proven *Bacteroides* osteomyelitis, occurring in the head of the right femur, was reported by Chandler and Breaks¹⁸. This infection, appearing in the case of a 12 year old white boy, probably originated from acute otitis media due to *Bacteroides*. The course was stormy and prolonged, leukocytosis and anemia persisting throughout the acute phase. Sequestrectomy was required to eradicate the lesion.

CASE 8—A 5 year old white boy was admitted to the Stanford University Hospitals on Aug 13, 1945. A mandibular mass had been present for one year. Some enlargement of the swelling had been noted for the three months previous to admission but had become particularly obvious four days before as the result of a fall on the involved area.

On entry, the temperature was 37.6 S (99.7 F). The sole contributory finding was a hard, bony, nontender mass, 2 cm in diameter, on the left anterior aspect of the mandible. Neither leukocytosis nor anemia were observed during the course except at one period, in February 1948, when a white blood cell count of 18,800 and a hemoglobin concentration of 10.5 Gm were recorded.

18 Chandler, F. A., and Breaks, V. M. Osteomyelitis of the Femoral Neck and Head Caused by *Bacterium Necrophorum* (*Bacillus Funduliformis*), J. A. M. A. **116** 2390 (May 24) 1941.

Roentgenograms confirmed the clinical impression of a bony tumor, and surgical excision of an osteoma was performed three days after entry. Persistent low grade fever, prolonged drainage of the wound and separation of the wound edges complicated recovery, but the response to penicillin was good. However, a fracture at the surgical site was observed within four months after the patient's dismissal. A chronic course of recurrent suppurative complications, requiring repeated surgical intervention and intensive chemotherapy, followed for over two years.

The patient reentered the hospital in July 1946 because of the breakdown of an old surgical incision. This lesion originated from a small pustule in the area. An infected bone graft was diagnosed. Purulent discharge and low grade fever persisted for nearly three months. The removal of sequestrums and the administration of over 5,000,000 units of penicillin were required before the infection subsided.

Two successive specimens of purulent drainage from the infected mandible, obtained on July 3 and July 6, revealed a large number of *Bacteroides* plus a moderate number of coagulase-positive *Staphylococcus aureus* and non-hemolytic streptococci. The staphylococcus was inhibited with 0.05 unit of penicillin per cubic centimeter, the streptococcus was sensitive to 0.1 unit of penicillin per cubic centimeter, and the *Bacteroides* was resistant to 0.1 unit of penicillin per cubic centimeter, the highest concentration of the antibiotic drug employed. A culture of material from a superficial abscess of the jaw on June 26, 1947, revealed a light growth of nonhemolytic streptococci. This organism was inhibited with 0.1 unit of penicillin per cubic centimeter.

Superficial purulent drainage complicated surgical intervention as recently as February 1948, but two cultures of material from the wound, made in March, were sterile and the status of the patient at the time of this report is quite satisfactory.

In this case, the correlation between the delayed response to penicillin therapy and the resistance in vitro of *Bacteroides* to the antibiotic drug is of interest. Furthermore, *Bacteroides*, isolated twice from the infected bone graft, was the predominant organism at that time. A sequestrectomy was required in this instance as in Chandler and Break's case.

CASE 9—A white man of 45 entered the hospital on March 8, 1941, because of nuchal pain and limitation of motion to the right for approximately three months. By the date of entry, a swelling on the right side of the neck, a sore throat, fever, chills and a slight obstruction to breathing had developed. A tender, nonfluctuant, indurated mass, 2 cm in diameter, was located on the right side on the neck.

Radiation therapy, surgical aspiration, immobilization of the neck and the administration of sulfonamide drugs induced no clearcut improvement. A biopsy of the mass on the ninth day after admission revealed stony-hard, avascular, gray-white, poorly circumscribed inflammatory tissue. Draining cervical sinuses appeared about one month after entry. A slight gain in weight and subjective improvement were noted during a three month interval in the hospital. The disease progressed after the patient's transfer to another institution, and cervical osteomyelitis was diagnosed. Death occurred eight months after the onset. Bronchopneumonia secondary to the cervical osteomyelitis was the apparent cause.

A diagnosis of tuberculosis had been tentatively eliminated by a roentgenologic examination and by results of cultures and animal inoculation. No organisms were isolated from the drainage on surgical aspiration. Numerous pleomorphic

alpha hemolytic *Bacteroides* were recovered on May 23, 1941 from pus obtained from the draining cervical sinuses. A few coagulase-positive *Staphylococcus aureus* organisms accompanied the *Bacteroides*.

The history of sore throat, fever and chills at the time of entry indicates that the pharynx, a common primary focus of *Bacteroides* infection, may have been the source of infection in this patient, followed by metastatic osteomyelitis of the spine. Tenderness, edema and even suppuration of the lateral aspects of the neck have been observed during the development of postanginal *Bacteroides* septicemia.^{8b}

Pulmonary Infections—In 1904, Guillemot and others¹⁹ reported the isolation of *Bacteroides* from purulent exudate in 11 of 13 cases.

TABLE 4—Cases of Pulmonary Infection in Which *Bacteroides* Was Isolated

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
10	45	F	W	Empyema	Thoracic pain, fever and signs of pleural effusion following esophageal perforation, sulfonamide drugs given throughout course, thoracotomy performed, 240,000 units penicillin given in 4 days after operation, death 3 weeks after entry	Many <i>Bacteroides</i> and a few <i>Staph albus</i> isolated from empyema at operation
11	46	M	W	Empyema	Fever, cough, sputum and thoracic pain (left) of 6 weeks' duration, good response to surgical drainage, penicillin given before entry and after operation, sulfonamide drugs given after operation, marked tendency to recurrent thrombophlebitis	<i>Bacteroides</i> sole organism recovered at time of rib resection; subsequent culture of empyema fluid revealed <i>Bacteroides</i> and nonhemolytic streptococci
12	43	M	W	Lung abscess	Severe cough, foul sputum and fever of 8 months' duration, treatment, including several major operative procedures and administration of much penicillin, of no definite benefit	Large numbers of <i>Bacteroides</i> accompanied by many anaerobic nonhemolytic streptococci and <i>Actinomyces</i> recovered from cavity of abscess on one occasion
13	43	M	W	Bronchiectasis	Severe illness marked by cough, foul sputum and extreme weakness of 10 months' duration, no response to heavy doses of penicillin, streptomycin and sulfadiazine, death immediately after pneumonectomy	<i>Bacteroides</i> plus anaerobic hemolytic and nonhemolytic streptococci and <i>Actinomyces</i> isolated from sputum
14	56	M	W	Postpneumectomy bronchial fistula	Cough, night sweats and hemoptysis of 1 year's duration found to be caused by bronchogenic carcinoma, temporary improvement after pneumonectomy, but death within 9 months	Gas producing <i>Bacteroides</i> present in postoperative pleural fluid in association with <i>Staph aureus</i> (coagulase positive)

of pulmonary infection (mainly putrid empyema). Later, Cohen²⁰ stated that pus recovered at operation yielded *Bacteroides* in 14 of 16 cases of abscess of the lung. Anaerobic diphtheroids and anaerobic nonhemolytic streptococci were found in all 16 specimens, aerobic bacteria being isolated in only 3 instances. It is of interest that suppurative pulmonary emboli have been reported to be a common occurrence in *Bacteroides* septicemias.²¹ Other studies have indicated the importance of anaerobic organisms in the pathogenesis of pulmonary suppuration.

¹⁹ Guillemot, L., Halle, J., and Rist, É. Recherches bactériologiques et expérimentales sur les pleuresies putrides, Arch de med exper et d'anat path 16 571, 1904

²⁰ Cohen, J. The Bacteriology of Abscess of the Lungs and Methods for Its Study, Arch Surg 24 171 (Feb) 1932

²¹ Lemierre² Lemierre, Reilly and Laporte^{8b}

Bacteroides was recovered in 2 cases of empyema, 1 of an abscess of the lung, 1 of bronchiectasis and 1 of postpneumectomy fistula in this study

CASE 10—Empyema, occurring in the case of a white woman of 45, was of unusual interest inasmuch as it seemed to be secondary to esophageal perforation following instrumentation with a Plummer bag. The empyema was characterized by pain in the right side of the thorax, fever and signs of pleural effusion. A stormy course followed and death occurred three weeks after the patient's entry. A variety of organisms, mainly nonhemolytic streptococci and *Staphylococcus aureus*, were recovered by aspiration, but *Bacteroides* was not isolated until a thoracotomy was performed. At that time, the fluid drained at operation contained an extremely heavy growth of *Bacteroides* and a few *Staphylococcus albus*. Sulfonamide drugs were given throughout the illness, and a total of 240,000 units of penicillin were administered during the four postoperative days. It may be more than a coincidence that *Bacteroides* were the final organism discovered prior to the patient's demise. Previous reports have commented on possible secondary fatal infection by *Bacteroides* in cases of debilitated patients¹⁷

CASE 11—The other case of empyema, in a white man of 46, was characterized by the acute onset of fever, cough, the production of sputum and pain in the left side of the thorax. Penicillin was administered prior to the patient's entry. *Bacteroides* requiring 0.2 unit of penicillin per cubic centimeter for inhibition was isolated in pure culture from operative material obtained at the time of resection of a rib. Penicillin and sulfonamide drugs were administered after the operation. The subsequent culture of the drainage from the empyema cavity revealed *Bacteroides* and an anaerobic nonhemolytic streptococcus. This case contrasts with case 10, since a good result followed surgical intervention.

OTHER CASES—Numerous other anaerobic organisms were recovered with *Bacteroides* from the lung abscess (case 12) and the site of the bronchiectasis (case 13). Operative material was the source of the organism in case 12. Intensive penicillin therapy was utilized in both cases, plus heavy doses of streptomycin and sulfadiazine in case 14. The recovery of *Bacteroides* did not coincide with the period of most intensive antibiotic therapy in either instance. The major organism recovered from the draining postpneumectomy fistula (case 13) was a coagulase-positive *Staphylococcus aureus*, there being a sparse growth of *Bacteroides*. Bronchogenic carcinoma was the primary disease. In this instance, the *Bacteroides* as cultured was definitely a gas former, but gas was not noted in the patient's tissues. The formation of the fistula and the presence of *Bacteroides* may have been related. Shaw²² observed the formation of a bronchial fistula following thoracotomy in a case of empyema, *Bacteroides* being recovered from the operative purulent material.

Otolaryngeal Lesions—*Bacteroides* has been implicated as an important etiologic agent in chronic suppurative otitis media. A recent report^{6a} mentioned its isolation in 2 such cases. Serious complications

²² Shaw, F. W., and Bigger, I. A. Necrobacillosis of the Lung, *J. A. M. A.* 102:688 (March 3) 1934.

ascribed to chronic purulent otitis media due to *Bacteroides* include generalized sepsis with bacteremia² and meningitis and brain abscess²³

This study contains reports of only 2 otolaryngeal cases

CASE 15—A woman of 45 had a severely inflamed right maxillary sinus which was discovered by antral puncture to contain pus from which *Bacteroides* was isolated in pure culture. Postnasal drip for five years, frontal headache for one and one-half years and the absence of relief after submucous resection marked the course prior to the patient's admission to the hospital. Considerable relief was gained by the puncture of the antrum.

CASE 16—The other patient entered the clinic because of chronic otorrhea on the right side following a simple mastoidectomy one year before. Subsequently, postauricular swelling indicated a serious exacerbation of mastoiditis and radical mastoidectomy was performed. The drainage of thick, green pus from the mastoidectomy wound complicated recovery, but the response to local treatment was good. *Bacteroides* was isolated once from the right ear as the drainage from the wound was subsiding, *Staphylococcus albus*, diphtheroids and hemolytic streptococci were recovered concurrently (hemolytic streptococcus was the sole organism isolated from the right ear on two prior occasions). It seems reasonable to conclude that *Bacteroides* was a secondary invader.

Infections of the Urinary Tract—Albarran and Cottet²⁴ reported the isolation of *Bacteroides* plus other anaerobic organisms and aerobic bacteria in 2 of 9 cases of pyelonephritis. Both cases were characterized by the presence of renal calculi. Two hundred grams of thick, fetid pus was obtained by ureteral catheterization in 1 of these cases. Also reported was the recovery of *Bacteroides* from 11 of 25 "urinary abscesses," perineal and periureteral infections being the main foci.

Bacteroides was isolated from the urine in 4 cases in this series. The organism was recovered in large numbers in 2 of these.

CASE 17—A woman of 24 experienced low grade fever, commencing one day after a normal delivery. This persisted, and tenderness over the breasts, the saphenous veins and the thighs developed two days later. A few white blood cells and marked bacteriuria were noted coincidentally with the beginning of fever. Pyelitis and possible thrombophlebitis were diagnosed. The patient received 8 Gm of sulfathiazole in one week and recovered. The single culture of the urine, performed four days after the onset of the illness and four days after the institution of sulfonamide therapy, revealed numerous *Bacteroides* and a few nonhemolytic streptococci.

CASE 18—The remaining case of heavy growth of *Bacteroides* in the urinary tract was that of a woman of 59, who had a history of renal infection on the right side and renal calculi of five years' duration. Other physicians had performed numerous diagnostic procedures and had given her repeated courses of sulfonamide drugs and penicillin. The most recent examination prior to admission had revealed the delayed appearance of dye from the right kidney and pyuria. Tenderness

23 Smith, McCall and Blake¹⁵ Ballenger, Schall and Smith¹⁶

24 Albarran, J, and Cottet, J. Des infections urinaires anaerobies, in *Cong internat de med profess*, de 1900, p 281

of the right costovertebral angle was elicited on the patient's entry. It was still present at the time of the second and final visit, eleven days later. Urinalysis revealed a slight trace of protein and 4 to 8 white blood cells per high dry field on entry. The only contributory finding eleven days later was 10 to 15 white blood cells per high dry field. An extremely heavy growth of *Bacteroides* in pure culture was recovered from the urine on entry and again eleven days later. The history of calculi may be significant since Albarran and Cottet²⁴ also observed them in both their cases of pyelonephritis with *Bacteroides* in the urine.

OTHER CASES—The isolation of *Bacteroides* from the urine seemed to be of lesser significance in the other 2 cases. In case 19, in which the condition was diagnosed as a possible postpartum pyelonephritis, 400 *Staphylococcus albus* per cubic centimeter and a few *Bacteroides* were recovered from the urine at the same time that sulfonamide and penicillin therapy was instituted. In case 20, a few *Bacteroides* were present in the urine of the patient, who had no other evidence of infection of the urinary tract.

Cutaneous and Other Superficial Lesions—Pustular eruptions of the skin have been observed in the course of bacteremic infection by *Bacteroides*.² A case of cutaneous abscesses of the hand acquired by a person in contact with an animal infected by *Bacteroides* has been described.²⁵ Little other concrete or detailed information about superficial *Bacteroides* infections is available.

CASE 21—A Negro aged 30 entered the hospital on July 18, 1946 with an eruption of the scalp of seven or eight months' duration. It commenced as a pruritic pimple which was first detected after the use of hot shot® hair dressing. A private physician prescribed a white salve, but it was without beneficial effect.

Fluctuant nodules and tumors were observed over the entire scalp with many areas of associated alopecia. Pus could readily be expressed from lesions in the right occipital region. Retroauricular and posterior cervical adenopathy were noted.

The laboratory data were noncontributory. No leukocytosis was noted.

A few coagulase-negative staphylococci (*Staph. albus*) were isolated from the draining lesions several times early in the course of the disease. The culture of material obtained by aspiration of an abscess about two months after the patient's entry revealed a heavy growth of *Bacteroides* plus a few anaerobic nonhemolytic streptococci and *Staphylococcus albus*. The culture of a similar lesion on November 17 revealed many gram-variable anaerobic organisms and a few *albus* organisms. The former were inhibited by 0.05 unit of penicillin per cubic centimeter and grew sparsely in 10 micrograms of streptomycin per cubic centimeter coincidentally with the period of penicillin therapy. The culture of purulent material on April 16, 1947 resulted in a moderately heavy growth of *Bacteroides*. The highest dilution of penicillin employed in this instance, 0.10 unit per cubic centimeter, had no inhibitory effect on *Bacteroides*. The last study, on October 2, again revealed *Bacteroides*. This very heavy growth was inhibited by 0.05 unit of penicillin per cubic centimeter.

²⁵ Stemen, C. M., and Shaw, F. W. Necrobacillosis of the Skin, *J. Kansas M. Soc.* **10**: 405, 1910.

Sulfadiazine (1 Gm every four hours for about three days) brought no improvement. Thereafter, numerous exacerbations of these relatively symptom-free lesions characterized the illness. All treatment, including surgical drainage and a regimen of 12,000,000 units of penicillin in oil and beeswax within thirty days, led to nothing more than quite temporary regression of the nodules and abscesses.

Bacteroides was probably the primary organism responsible for this unusual infection. Despite the absence of generalized toxicity, the condition was extraor-

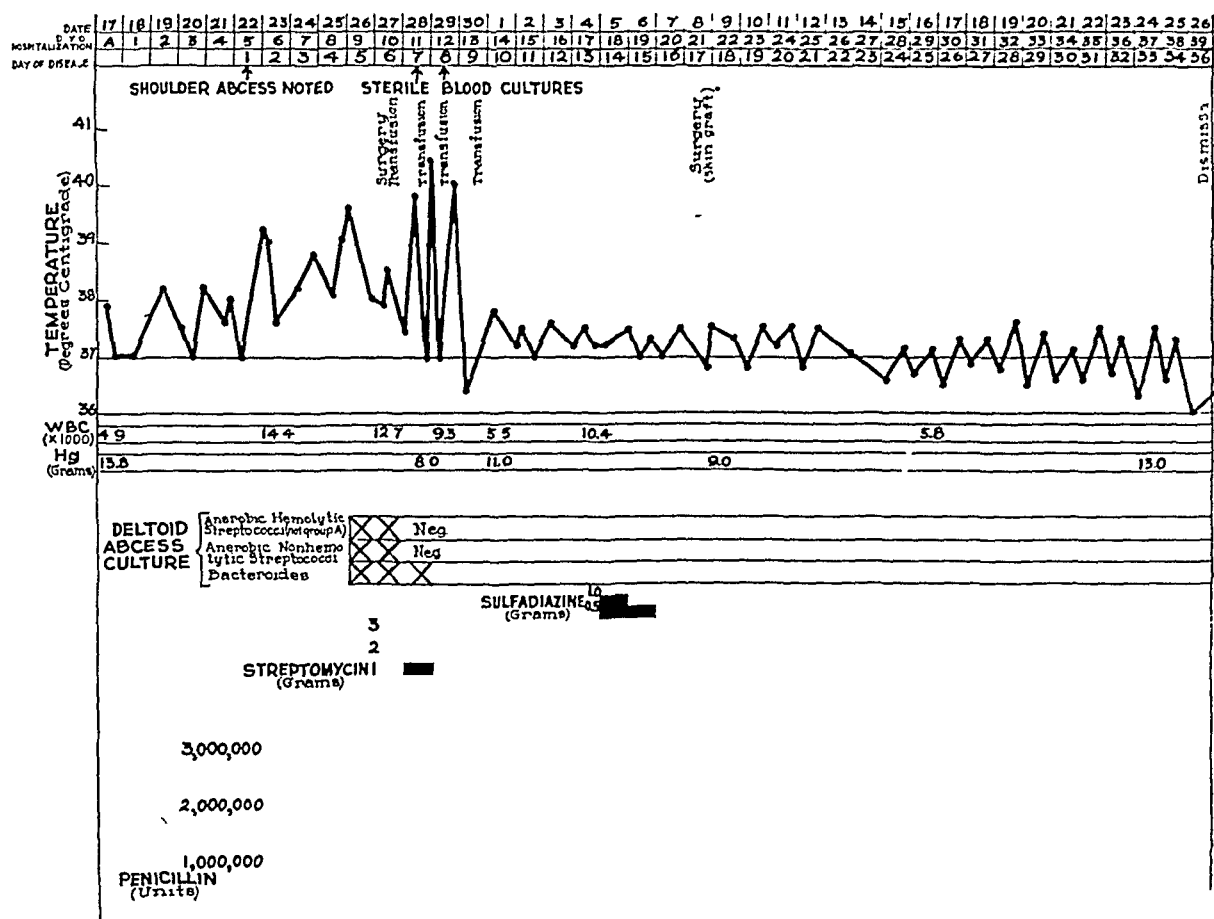


Chart 5—Course in case 22 (abscess of the left deltoid muscle)

dinarily refractory to treatment. Neither repeated surgical drainage nor moderate amounts of penicillin seemed to have more than a transient beneficial effect.

CASE 22—Another severe infection was that of a white woman of 25 (chart 5) who had a deltoid abscess from which *Bacteroides* was isolated three times, once alone. About two weeks of intensive therapy was required to bring the infection under control. A total of nearly 30,000,000 units of penicillin and 17 Gm of streptomycin were administered. Radical débridement was performed because the abscess possessed the clinical and roentgenologic attributes of gas gangrene at one stage of the illness. Gas gangrene antitoxin and 15 Gm of sulfadiazine were also prescribed. Pronounced anemia persisted throughout the acute phase of the disease.

CASE 23—A heavy growth of *Bacteroides* was recovered from the draining sinuses of a woman of 18 with suppurative hidradenitis of the axillas. Numerous coagulase-negative staphylococci (*Staph. albus*) *albus* and a few nonhemolytic streptococci were isolated concurrently. Boils of the axillas had been present for two years prior to the entry of the patient, but the response to therapy, including the administration of penicillin and hot soaks, had been poor. Severe facial acne accom-

TABLE 5—Cases of Cutaneous and Other Superficial Lesions in Which *Bacteroides* Was Isolated

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
21	30	M	N	Scalp abscesses	Recurrent abscesses of scalp resistant to all treatment, including 12,000,000 units of penicillin within 1 month and repeated surgical drainage, case followed over 2 years	<i>Bacteroides</i> isolated on only 2 occasions
22	25	F	W	Left deltoid abscess	Patient showed poor control of diabetes on entry, with fever, painful left shoulder and hot, tender abscess, clinical and roentgen evidence of gas gangrene, operation and high dosage of antibiotic drugs brought slow recovery, severe anemia in acute stage	<i>Bacteroides</i> recovered on 1 separate occasions, the third in pure culture after administration of penicillin, <i>Clostridium</i> not present
23	18	F	W	Hidradenitis suppurativa	Boils of axillas and facial acne for 2 years, no response to parenteral administration of penicillin, temporary remission with irradiation and local penicillin therapy, but recurrence of infection of left axilla in 1 month, draining sinuses on entry	Heavy growth of <i>Bacteroides</i> and coagulase-negative <i>Staph. albus</i> , plus a few nonhemolytic streptococci from draining sinuses
24	2	F	W	Abscesses of right groin and thigh	Scant, milky, sanguinous material aspirated from abscesses, leukocytosis and anemia present, response to surgical drainage and penicillin therapy, death due to medulloblastoma	Culture revealed only <i>Bacteroides</i> in both lesions
25	42	F	W	Parotitis	Parotitis discovered in course of work up for cause of abdominal pain, fever and nausea and vomiting in a case of diabetes, <i>Esch. coli</i> bacteremia and enterococcal bacteriuria major findings	<i>Bacteroides</i> isolated once concurrently with 3 other genera of bacteria
26	36	M	W	Left pararectal abscess	Abscess of 1 month's duration responded rapidly to surgical drainage, similar lesion noted 15 years earlier	<i>Bacteroides</i> and coagulase-negative <i>Staph. albus</i> only organisms observed
27	21	F	N	Left pararectal abscess	Deep vaginal tear following delivery with forceps later, fever and anal pain, relief by incision and drainage	<i>Bacteroides</i> 1 of 3 organisms isolated
28	52	F	W	Breast abscess	Painful mass in left breast of 4 days' duration, good response to surgical drainage	<i>Bacteroides</i> and anaerobic nonhemolytic streptococci recovered
29	12	F	N	Abscess of sebaceous cyst superior to ear	Mass above right ear present for 1 year with recurrence and enlargement 2 weeks before entry, recession following incision and drainage	<i>Bacteroides</i> and nonhemolytic streptococci only organisms isolated
30	34	M	N	Left inguinal abscess	Gonorrhea treated with penicillin prior to onset of adenopathy, enlargement of left inguinal lymph node, rapid regression following aspiration	<i>Bacteroides</i> and anaerobic nonhemolytic streptococci recovered
31	22	F	W	Pilonidal cyst abscess	Tender abscess at base of sacrum present for 4 days, good response to surgical drainage	Heavy growth of <i>Bacteroides</i> , two other organisms in small numbers
32	61	M	W	Pyodermic ulcer of left leg	Pyodermic ulcer decreased in size and improved in appearance within 10 days after administration of penicillin, débridement and local therapy	Heavy growth of <i>Bacteroides</i> coagulase negative <i>Staph. aureus</i> , hemolytic streptococci and <i>O. welchii</i>

panied the onset of the hidradenitis and persisted. Two million seven hundred thousand units of penicillin administered at this hospital were of no avail. However, local radiation therapy and 3,600,000 units of penicillin injected directly into the axillas brought marked improvement. This regimen was continued after the patient's discharge from the hospital, but severe infection of the left axilla nevertheless recurred about one month later. This report parallels a description of a case of suppurative hidradenitis of nineteen years' duration, reported by Smith and Ropes,^{6a} from which *Bacteroides* was repeatedly isolated in mixed culture with

staphylococci or streptococci. In Smith and Rope's case, the buttocks, chest, back and face had also been involved at various stages of the disease.

CASE 24—Abscesses of the groin and thigh in the case of a child of 2 demonstrated a delay in response to surgical drainage and the administration of penicillin. The infection was of minor importance in comparison with the fatal medulloblastoma in this case. The pus expressed from the lesions was of a scanty, milky, sanguinous appearance rather than being of the bulky, foul, gray-green variety usually described in abscesses due to *Bacteroides*.

CASE 25—Although few in number, the *Bacteroides* discovered in this case of parotitis may have been of greater importance than a first glance at the data would indicate. The *Bacteroides* and anaerobic nonhemolytic streptococci, although quite sparse, were the most penicillin resistant of the flora. Antibiotic therapy and chemotherapy were begun following the isolation of *Bacteroides*, it was not recovered subsequently.

OTHER CASES—The remainder of the conditions, including 2 pararectal abscesses (cases 26 and 27), an abscess of the breast (case 28), an abscess of the ear area (case 29), an abscess of an inguinal lymph node (case 30), an abscess of a pilonidal cyst (case 31) and a pyodermic ulcer of the leg (case 32), were relatively mild and responded well to simple surgical drainage, the administration of antibiotic drugs or local therapy. It is perhaps noteworthy that the patients in 2 of the 12 cases of superficial lesions (those of the severe deltoid abscess [case 22] and of the parotitis [case 25]) had diabetes.

Infection of the Female Genital Tract—*Bacteroides* is a common saprophyte of the female genital tract.²⁶ It has been implicated mainly as a secondary invader in chronic and subacute pathologic processes of this system, but its importance in puerperal fever has been indicated.^{26b} Severe and even fatal puerperal infection, particularly following deliveries complicated by operative intervention, has been attributed to *Bacteroides*.²⁷

Bacteroides was the lone organism isolated in the present series from most of the circumscribed lesions of the female genital tract, accompanying bacteria being present in only 3 of the 7 cases described.

Three cases of tubo-ovarian abscess requiring surgical intervention were examples of serious invasion of the genital tract by *Bacteroides*.

CASE 33—A white woman aged 21 had a history of a ruptured appendix one year previously with an apparently good response to surgical intervention. Chills, fever, lower abdominal pain and a mass in the right adnexa were noted two months prior to entry. Rest, the administration of sulfonamide drugs and the incision and drainage of the mass brought periods of remission, but exacerbations followed. A mass developed in the left fallopian tube, and, about five months after entry, a subtotal hysterectomy, a bilateral salpingectomy and a left oophorectomy were performed during a quiescent phase of the illness. Convalescence was uneventful.

26 (a) Lemierre² (b) Burdon, K. L. *Bacterium Melaninogenicum* from Normal and Pathologic Tissues, *J. Infect. Dis.* **42** 161, 1928.

27 Harris, J. W., and Brown, J. H. Description of a New Organism That May Be a Factor in the Causation of Puerperal Infection, *Bull. Johns Hopkins Hosp.* **40** 203, 1927.

Leukocytosis and anemia were present throughout the acute course. A pure culture of *Bacteroides* was recovered from the tubo-ovarian abscess on the left side, discovered at operation. The possibility was entertained that the illness had actually been initiated by a retained portion of the ruptured appendix.

CASE 34—The second example of tubo-ovarian abscess occurred in the case of a woman of 29 who entered the hospital with a history of vaginal hemorrhage, dysuria and lower abdominal pain for one week. Slight improvement had

TABLE 6—Cases of Circumscribed Lesions of the Female Genital Tract in Which *Bacteroides* Was Isolated

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
33	21	F	W	Left tubo-ovarian abscess	Appendicitis and appendectomy 1 year before entry, chills, fever, pain and mass in right lower quadrant of abdomen for 2 months before, leukocytosis and anemia present, 74 Gm of sulfonamide drugs given in 2 months, subtotal hysterectomy, bilateral salpingectomy and left oophorectomy 4 months after entry	<i>Bacteroides</i> recovered in pure culture from tubo-ovarian abscess discovered at operation
34	29	F	W	Right tubo-ovarian abscess	Lower abdominal pain, vaginal hemorrhage, dysuria and fever for 1 week, sulfonamide drugs given prior to entry, mass in cul de sac and, later, in right lower quadrant palpated, subtotal hysterectomy, bilateral salpingectomy and right oophorectomy performed 6 months after entry	<i>Bacteroides</i> recovered in pure cultures from abscess at operation
35	23	F	W	Tubo-ovarian abscess	Induced abortion about 4 months before entry, vaginal hemorrhage, lower abdominal pain and fever marked course, on entry, tenderness in lower abdomen and mass in right adnexa, penicillin and sulfadiazine no aid, excision of abscess and cornual portion of right tube	<i>Bacteroides</i> and anaerobic nonhemolytic streptococci isolated from tubo-ovarian abscess at time of operation
36	23	F	N	Cul de sac abscess	History of gonorrhea 1 year before entry, recurrent episodes of pain and tenderness in lower abdomen of 4 months' duration, mass in right adnexa on entry, 200,000 units penicillin given 6 days before isolation of <i>Bacteroides</i> , colpotomy of cul de sac abscess at that time (2 years after admission)	<i>Bacteroides</i> recovered in pure culture from abscess of cul de sac
37	46	F	W	Bartholinian abscess	Painless lump on vulva for 3 weeks prior to entry, persisted for next 7 months despite repeated surgical drainage, no antibiotic therapy or chemotherapy	Pure culture of <i>Bacteroides</i> recovered from Bartholinian abscess
38	48	F	N	Right vulval ulcer	Small mass noted on right side of vulva 7 years before entry, ulcer developed which was resistant to therapy, intensive sulfonamide therapy prior to positive culture, painful swelling present on right side of vulva 25 years earlier	<i>Bacteroides</i> , <i>Staph aureus</i> and nonhemolytic streptococci isolated from ulcer
39	17	F	W	Vaginal abscess	Vaginal discharge for 4 months, congenital stricture of vagina, 300 cc pus drained surgically, relief after surgery, postoperative penicillin therapy	<i>Bacteroides</i> predominant organism, very few staphylococci and nonhemolytic streptococci recovered
40	52	F	W	Paraurethral abscess	Pain and burning on urination for 2 weeks, relief after surgical drainage, previous history of treated gonorrhea, sulfonamide drugs given at time of surgical procedure	A few <i>Bacteroides</i> only organisms isolated from paraurethral abscess

followed the administration of about 3 Gm of sulfathiazole on the previous day. Fever and a mass in the cul-de-sac were the principal findings on admission. Rapid improvement followed with symptomatic therapy. Two and one-half months later, the patient reentered with an acute exacerbation of lower abdominal pain and with a mass in the right lower quadrant. Diathermy brought relief, but reentry with a similar episode occurred three months later and subtotal hysterectomy, bilateral salpingectomy and oophorectomy on the right were performed at this time. A tubo-ovarian mass and chronic inflammation were present on the right side. A pure culture of *Bacteroides* was isolated from the tubo-ovarian mass. The laboratory findings were noncontributory, aside from a single slightly elevated white blood cell count.

CASE 35—The third example of tubo-ovarian abscess, in the case of a woman of 23, followed an induced abortion. A hemorrhage immediately followed instrumentation with a catheter, while fever and lower abdominal pain commenced ten days later, these symptoms continued until admission. Moderate tenderness in the lower part of the abdomen and a mass in the right adnexa were present. The temperature was 37.2 C (99.0 F) and remained normal although the patient reported that a temperature of 102 F had been present prior to entry. The white blood cell count was 16,000 cells per cubic millimeter of blood. The pain persisted and the mass enlarged despite the administration of 1,650,000 units of penicillin within one week and of 8 Gm of sulfadiazine within three days. Dilation and curettage and exploratory laparotomy were performed nine days after entry. A tubo-ovarian abscess was observed on the right side, this, plus the cornual portion of the fallopian tube, was excised. A week later, the patient was dismissed in good condition. *Bacteroides* and anaerobic nonhemolytic streptococci were isolated from the tubo-ovarian abscess.

The foregoing 3 cases simulated gonococcal salpingitis. They were reminiscent of a case of *Bacteroides* salpingitis and peritonitis (no 6 in the series reported by Smith and Ropes^{6a}).

CASE 36—In this case of abscess of the cul-de-sac, the patient had a history of possible gonorrhea about one year prior to entry. Episodes of lower abdominal pain recurred, as did adnexal masses, during a two year period before the abscess was outlined. The illness, at the time of the appearance of the mass in the cul-de-sac, was associated with chills, fever and lower abdominal pain, all of which subsided after a posterior colpotomy. Approximately 1,000,000 units of penicillin in one week and sulfonamide in the customary dosage were administered in concert with the surgery. *Bacteroides* was the only organism recovered from the abscess. *Bacteroides* may have been a late invader, *Neisseria gonorrhoeae* being the likely primary etiologic agent.

OTHER CASES—Another history of gonorrhea, confirmed in this instance, preceded the onset of a paraurethral abscess (case 37). Sulfathiazole was administered concurrently with surgical drainage, but resolution of the lesion seemed to be due to the operation. The drug was given prior to the isolation of *Bacteroides* in a case of vulval ulcer (no 38) and led to no marked improvement. Penicillin was prescribed after successful surgical drainage of the vaginal abscess in case 39. No antibiotic therapy or chemotherapy was administered to the patient with a Bartholinian abscess (case 40), the lesion persisted for six months despite repeated aspiration.

Seven cases of infection of the uterine tract were characterized by the presence of *Bacteroides* in the uterine or vaginal discharge. Five of the 7 cases were examples of postpartum infection. In case 41, *Bacteroides* was penicillin resistant in contrast to the single other organism, a nonhemolytic streptococcus, which was penicillin sensitive. Penicillin and sulfonamide drugs, alone or in combination, were given in all 5 cases. Four patients improved rapidly, but recovery in case 42 was complicated by postpartum hemorrhage, anemia, cervicitis and endometritis. A long-standing vaginal discharge and a recent bout of vaginal hemorrhage characterized 1 nonparturient case (no 43). The discharge gradually abated, the administration of diethylstilbestrol being of apparent aid. In the other nonparturient case (no 44), the patient had a vaginal discharge of two weeks' duration which apparently subsided spontaneously. Only slight inflammation of the vagina had been noted at the time of admission.

Seven examples of probable saprophytic *Bacteroides*²⁶ within the female genital tract were observed in this study. The need for more active study of the role of *Bacteroides* in uterine infection, particularly in the "postpartum state," is evident.

TABLE 7—Cases in Which *Bacteroides* Was Isolated from Urine and Vaginal Discharge

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
41	19	F	W	Uterine discharge	Postpartum fever, tenderness of uterine fundus, costovertebral tenderness and foul lochia, improvement after administration of 240,000 units of penicillin in 1 day	Penicillin resistant <i>Bacteroides</i> principal organism recovered, few penicillin sensitive nonhemolytic streptococci also present
42	31	F	W	Uterine discharge	Patient febrile before and after delivery, hemorrhage and severe anemia immediately post partum, abdominal pain and vaginal discharge due to subacute and cystic cervicitis occurred 10 weeks post partum, no antibiotic therapy or chemotherapy	<i>Bacteroides</i> and anaerobic nonhemolytic streptococci isolated
43	65	F	N	Uterine discharge	Long standing vaginal discharge and recent vaginal hemorrhage, cessation of discharge after diethyl stilbestrol treatment. No antibiotic therapy or chemotherapy	<i>Bacteroides</i> and anaerobic nonhemolytic streptococci isolated
44	5	F	W	Vaginal discharge	Vaginal discharge for 2 weeks, only slight inflammation of vagina at time of entry, spontaneous remission without therapy	Heavy growth of <i>Bacteroides</i> , <i>Staph albus</i> , nonhemolytic streptococcus and <i>Cl welchii</i>
45	16	F	N	Uterine discharge	Fever and retention of membranes post partum, fever disappeared 2 days after start of sulfadiazine therapy (4 Gm daily)	Pure culture of <i>Bacteroides</i> , blood culture negative
46	17	F	W	Uterine discharge	Postpartum fever and burning on urination, <i>Fsch coli</i> present in urine, good response to sulfonamide and penicillin therapy	Many <i>Bacteroides</i> and few <i>Staph albus</i> isolated
47	29	F	W	Uterine discharge	Fever accompanied postpartum retention of membranes, temperature normal within 1 day of commencement of penicillin therapy	<i>Bacteroides</i> and anaerobic nonhemolytic streptococci isolated

TABLE 8—Organisms Isolated Coincidentally with *Bacteroides*

Cases in which pure culture of <i>Bacteroides</i> was obtained	13
Cases in which mixed cultures were obtained	34
Anaerobic nonhemolytic streptococcus	16
Nonhemolytic streptococcus	11
<i>Staph albus</i>	10
<i>Staph aureus</i> (coagulase positive)	7
Anaerobic hemolytic streptococcus	4
Hemolytic streptococcus	3
Coliform bacilli	3
Diphtheroids	1
<i>Pneumococcus</i> (type V)	1
<i>Pseudomonas aeruginosa</i>	1
<i>Alcaligenes faecalis</i>	1
<i>Actinomyces</i>	1
Coagulase negative <i>Staph aureus</i>	1
<i>Cl welchii</i>	2

ACCOMPANYING FLORA

A brief survey of the organisms isolated concurrently with *Bacteroides* is presented in table 8. The high incidence of anaerobic streptococci, particularly of the nonhemolytic variety, seems to be more than fortuitous. Frequent association of anaerobic streptococci with

Bacteroides has been observed in other studies,²⁸ and the possibility of a symbiotic relationship between *Bacteroides* and anaerobic streptococci has been suggested²⁹

TREATMENT

The treatment of infection by *Bacteroides* has included administration of potassium iodide,³⁰ vigorous aeration of local lesions,³¹ the administration of sulfonamide drugs,³² streptomycin³³ and penicillin,² surgical drainage³⁴ and ligation of thrombosed veins, particularly of the internal jugular vein in septicemias^{3b}. Definite value has been attributed to intensive treatment with sulfonamide drugs, particularly sulfapyridine, however, its beneficial effects have been noted to be irregular.² The importance of supportive therapy, particularly blood transfusions and the parenteral administration of fluids, has been emphasized.¹⁰

Surgical drainage was usually effective for the management of accessible localized lesions in cases of this study. There were exceptions, of which examples were case 21 (scalp abscesses) and case 40 (repeatedly occurring bartholinian abscess).

In a recent review of septicemias due to *Bacteroides funduliformis*, Lemierre² claimed the administration of penicillin to be a most efficacious means of combating this infection, having observed a remarkable therapeutic effect in several critical cases. Varying degrees of refractoriness to penicillin therapy were displayed in the present series. Bacteremia (case 1) and recurrent abscesses of the scalp (case 21) were not benefited by prolonged courses of penicillin. A compilation of penicillin sensitivities in vitro is interesting when correlated with clinical effects (see table 9).

Unfortunately, many of the sensitivity studies were not carried out beyond a concentration of 0.10 unit of penicillin per cubic centimeter. Furthermore, a number of specimens were not tested because of technical difficulties in culturing *Bacteroides*. It is clear, nevertheless, that the organism may be resistant to penicillin since 7 of 9 organisms tested displayed some degree of refractoriness to this antibiotic drug. Our

28 Lemierre, Reilly and Laporte^{3b} Cohen²⁰

29 Cohen²⁰ Norris, C. Suppurative Pyelophlebitis Associated with Anaerobic Micro-Organisms, *J. M. Research* **6** 97, 1901

30 Shaw, F. Human Necrobacillosis, *Zentralbl. f. Bakt.* **129** 132, 1933

31 Martin, W. B. Human Infection with *B. Necrophorum*, *Am. J. Clin. Path.* **10** 567, 1940

32 Brown, A. E., Williams, H. L., and Herrell, W. E. *Bacteroides* Septicemia. Report of a Case with Recovery, *J. A. M. A.* **116** 402 (Feb. 1) 1941

33 Cressy, N. L., Lahey, W. J., and Kunkel, P. Streptomycin in the Treatment of Bacterial Endocarditis, *New England J. Med.* **239** 497, 1948

34 Smith and Ropes^{6a} Lemierre, Reilly and Laport^{3b}

data support Foley's demonstration³⁵ of the penicillin resistance of *Bacteroides* in vitro, 12 strains being uninhibited by 100 units of penicillin per cubic centimeter, and Dienes' observation^{4b} that the L forms of *Bacteroides* are penicillin resistant. Clinical experience with the use of penicillin in *Bacteroides* infections is inadequate, but it is apparent that reliance on penicillin exclusively in such infections is not justifiable.

It has been claimed that streptomycin probably aided recovery in a case of *Bacteroides* endocarditis³³, large doses of penicillin and sulfonamide drugs were given after streptomycin therapy was begun. However, the in vitro sensitivities of 12 strains of *Bacteroides*, ranging from 750 to 2,000 micrograms of streptomycin per cubic centimeter,

TABLE 9—*Penicillin Sensitivity of Nine Strains of Bacteroides in Vitro*

Case	Source	Units Per Cc	Comment
1	Blood	Resistant, 0.4	Patient febrile for 3 weeks, over 6,000,000 units penicillin administered
2	Blood	Resistant, 6	Esch coli, predominant organism, streptomycin sensitive when <i>Bacteroides</i> resistant to 50 units streptomycin per cc, death due to bacteremia and pyelophlebitis despite administration of more than 40,000,000 units penicillin and 19 Gm streptomycin
5	Retroperitoneal abscess	Sensitive, 0.05	Rapid downhill course with death due to the retroperitoneal sarcoma
7	Osteomyelitis of mandible	Resistant, 0.1	Response to surgical intervention and 5,000,000 units penicillin delayed
10	Empyema	Sensitive, 0.2, resistant, 0.1	Response to rib resection and tube drainage good
20	Abscesses of scalp	April 16, 1947 resistant, 0.1, October 2 sensitive, 0.05	Recurrent scalp abscesses present over 2 years, resistance to repeated surgical drainage and to 12,000,000 units penicillin administered in 1 month
29	Parotitis	Resistant, 0.1	<i>Bacteroides</i> not predominant organism
37	Uterine discharge	Resistant, 0.1	<i>Bacteroides</i> likely etiologic agent in postpartum uterine infection

indicated basic streptomycin resistance by this organism³⁵. The value of the streptomycin used in the treatment of a few cases in the present study could not be determined. In case 2 (bacteremia), the single specimen of *Bacteroides* was resistant to 50 micrograms of streptomycin per cubic centimeter, and intensive streptomycin therapy did not prevent fatal termination. This agent may have played a role in the successful treatment of the deltoid abscess (case 22) and the meningitis (case 3).

COMMENT

In this series of cases of *Bacteroides* infection, the areas of predilection were the female genital tract and the superficial parts of the body. Bacteremia, meningitis, pulmonary infection, osteomyelitis, abdominal

35 Foley, G. E. In Vitro Resistance of the Genus *Bacteroides* to Streptomycin, *Science* **106** 423, 1947.

abscesses, maxillary sinusitis and infections of the urinary tract were other varieties of *Bacteroides* infection observed. Major lesions caused by *Bacteroides* described elsewhere, but not observed within the Stanford University Hospitals, included endocarditis,³⁴ appendicitis,^{13b} chronic ulcerative colitis³⁶ and possibly those of Reiter's disease^{6a}

A considerable number of *Bacteroides* infections have undoubtedly been overlooked in this hospital. Bacteremias and septicemias in particular have probably been missed. Whereas common technics are of some value,³⁷ the effective isolation of *Bacteroides* from the blood stream requires special anaerobic methods.⁶ Even highly specialized anaerobic technics of blood culture may not suffice for the recognition of mild, atypical bacteremias, which are commoner than was previously supposed.² Considerable diagnostic aid by a serum flocculation method purportedly specific for *Bacteroides funduliformis* antibodies has been reported.³⁸ An alcoholic extract of the organism is the antigen employed.

Metastatic, suppurative local lesions may occur during generalized sepsis,^{8b} as the result of infected emboli arising in a suppurative form of thrombophlebitis. Mild, evanescent bacteremias, often not recognized, have been stated to result in commonly observed small, isolated abscesses.² The original foci of *Bacteroides* bacteremias are supposedly in areas where *Bacteroides* maintain a saprophytic existence within the natural cavities of the body.³⁹ However, evidence suggesting exogenous infection by means of contaminated water has been presented.^{6b} Transmission of the organism from patient to patient has been indicated.⁴⁰ In a group of soldiers, deep gunshot wounds became infected by *Bacteroides* in a hospital. It has been stated that secondary infection is commonly caused by *Bacteroides*,^{20b} particularly in neoplastic disease.¹⁷ This study tended to support the validity of these claims.

The formation of gas by *Bacteroides* in culture has been demonstrated.⁴¹ One instance of gas formation in vitro was observed in this series (by the organism isolated in case 14). Cunningham⁴² noted the

36 Dack³ Dack, G M, Dragstedt, L R, and Heinz, T E. *Bacterium Necrophorum* in Chronic Ulcerative Colitis, *J A M A* **106** 7 (Jan 4) 1936

37 Pham^{6b} Waring, J J, Ryan, J G, Thompson, R, and Herrell, W E. *Bacteroides* Septicemia. Report of Case with Recovery, *Laryngoscope* **53** 717, 1943

38 Lemierre² Laporte, A, and Brocard, H. La réaction de flocculation du serum en presence d'un extrait alcoolique microbien dans les infections a *Bacillus funduliformis*, *Compt rend Soc de biol* **131** 4, 1939

39 Smith and Ropes^{6a} Lemierre^{8b}

40 Bogdan, A. Eine bisher unbekannte Infektionskrankheit bei Verwundeten, *Med Klin* **12** 383, 1916

41 Chandler and Breaks¹⁸ Harris and Brown²⁷

42 Cunningham, J S. Human Infection with *Actinomyces Necrophorus*. Bacteriologic and Pathologic Report of Two Cases Terminating Fatally, *Arch Path* **9** 843 (April) 1930

presence of gas, both clinically and roentgenologically, in a case of retropharyngeal abscess due to *Bacteroides* which terminated fatally. The presence of gas in the tissues of the arm was noted by Smith and Ropes⁶¹ during the course of a fatal sepsis. Clinically, typical gas gangrene with roentgen evidence of gas in the tissues was observed in case 22 of the present series. This evidence indicates that *Bacteroides* infection must be considered in the differential diagnosis of gas gangrene.

Available data indicate that *Bacteroides* is resistant to penicillin and streptomycin, and evidence in this study suggests that the clinical response to the administration of these antibiotic drugs may be poor. Consideration must be given to the possibility of superimposed or concomitant infection by penicillin-resistant *Bacteroides* or other organisms complicating the treatment of disease presumably caused by penicillin-sensitive bacteria.⁴³

SUMMARY

1 *Bacteroides* was recovered in 47 cases. A considerable variation in the severity of disease caused by this organism was demonstrated.

2 The most common sources were localized superficial lesions and the female genital tract. *Bacteroides* was also isolated in cases of bacteremia, meningitis, empyema, lung abscess, bronchiectasis, infection of the urinary tract, chronic otitis media, maxillary sinusitis, osteomyelitis, cervical sinuses, abdominal abscesses and thyroiditis.

3 *Bacteroides* was frequently isolated in pure culture, but the concurrent recovery of anaerobic streptococci was of significant frequency.

4 *Bacteroides* has gas-forming tendencies and may produce lesions which simulate those of gas gangrene.

5 There is clinical and laboratory evidence that a considerable degree of resistance to penicillin and streptomycin may be an important characteristic of *Bacteroides*.

43 Weinstein, L. The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin, *Am J M Sc* **214** 56, 1947. Appelbaum, E., and Leff, W. A. Occurrence of Superinfections During Antibiotic Therapy, *J A M A* **138** 119 (Sept 11) 1948.

MYOCARDIAL INFARCTION

Observations on One Hundred Patients Who Survived up to Six Years

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IN 1947, Mintz and Katz ¹ published observations on a large series of patients with recent myocardial infarction and pointed out features of importance in establishing the immediate prognosis. Recently, we ² analyzed the factors involved in determining the long term prognosis. During the latter study, a follow-up survey was made on 100 patients who had survived acute myocardial infarction from one to six years. The present report correlates the degree of electrocardiographic restitution following acute infarction with the clinical state of the patient.

The necessary data were obtained for 100 patients of the 507 whose cases had previously been reported. Of these, 84 were interviewed and examined at the hospital, for the remaining 16, follow-up information and electrocardiograms were obtained from the records of their private physicians. In every instance, a new electrocardiogram was taken and interpreted by us.

Almost all the patients interviewed were maintained on a regimen of combinations of barbiturates, papaverine and/or glyceryl trinitrate. One patient in the fourth decade who was addicted to the use of morphine had been treated for the habit before infarction. Most of the patients had returned to their former jobs and were working about the same number of hours as before infarction. In most instances, the younger patients were able to resume a fuller share of activity after recovery than the

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1 Mintz, S S, and Katz, L N. Recent Myocardial Infarction. An Analysis of Five Hundred and Seventy-Two Cases, *Arch Int Med* **80** 205 (Aug) 1947

2 Katz, L N, Mills, G Y, and Cisneros, F. Observations on the Survival of Patients After Recent Myocardial Infarction, to be published

older ones This was also observed by Cooksey,³ Master and Dack⁴ and others⁵

TYPES OF ELECTROCARDIOGRAPHIC RESTITUTION

Patients were classified according to the degree of recovery shown in follow-up electrocardiograms Three classifications were used

1 *Little Electrocardiographic Restitution* (figure, A) —The electrocardiograms for this group showed changes similar to those observed at the time of infarction, with characteristic coronary contours of the S-T segment of the T wave and of the QRS complex The coronary patterns were obvious and could readily be classified into one of the types previously recognized by one of us (L N K)⁶

2 *Partial Electrocardiographic Restitution* (figure, B) —The electrocardiograms for this group showed the QRS complex, and sometimes the T wave, characteristic of the coronary patterns, but without the deviations in the S-T segment Thus, there had been some return toward normal

3 *Complete Electrocardiographic Restitution* (figure, C) —The electrocardiograms for this group were similar to the control records, were within normal limits or, if abnormal, showed no stigma of coronary insufficiency

The groups with little and partial restitution were those to which we gave the electrocardiographic designation of chronic coronary insufficiency

RELATIONSHIP OF ELECTROCARDIOGRAPHIC RESTITUTION TO CLINICAL FINDINGS

1 *Little Electrocardiographic Restitution* —Seventy-seven of the 100 patients (59 males and 18 females) had little electrocardiographic restitution Twenty-four of these had no evidence of angina, hypertension or heart failure In the follow-up, hypertension occurring alone was the most frequent finding (16 cases), with angina pectoris, it accounted for the most frequent combination (15 cases) Angina pectoris alone accounted for 11 cases Heart failure was observed alone in 1 case, and in various combinations in the remaining 10 None of the patients had heart failure as an isolated disorder on admission to the hospital, but in the 3 instances in which it was present at that time it was associated with angina or hypertension Twelve patients had heart failure at follow-up, and for 11 of these the electrocardiograms showed little restitution

2 *Partial Electrocardiographic Restitution* —Fourteen patients (9 males and 5 females) had partial electrocardiographic restitution at follow-up Four of these

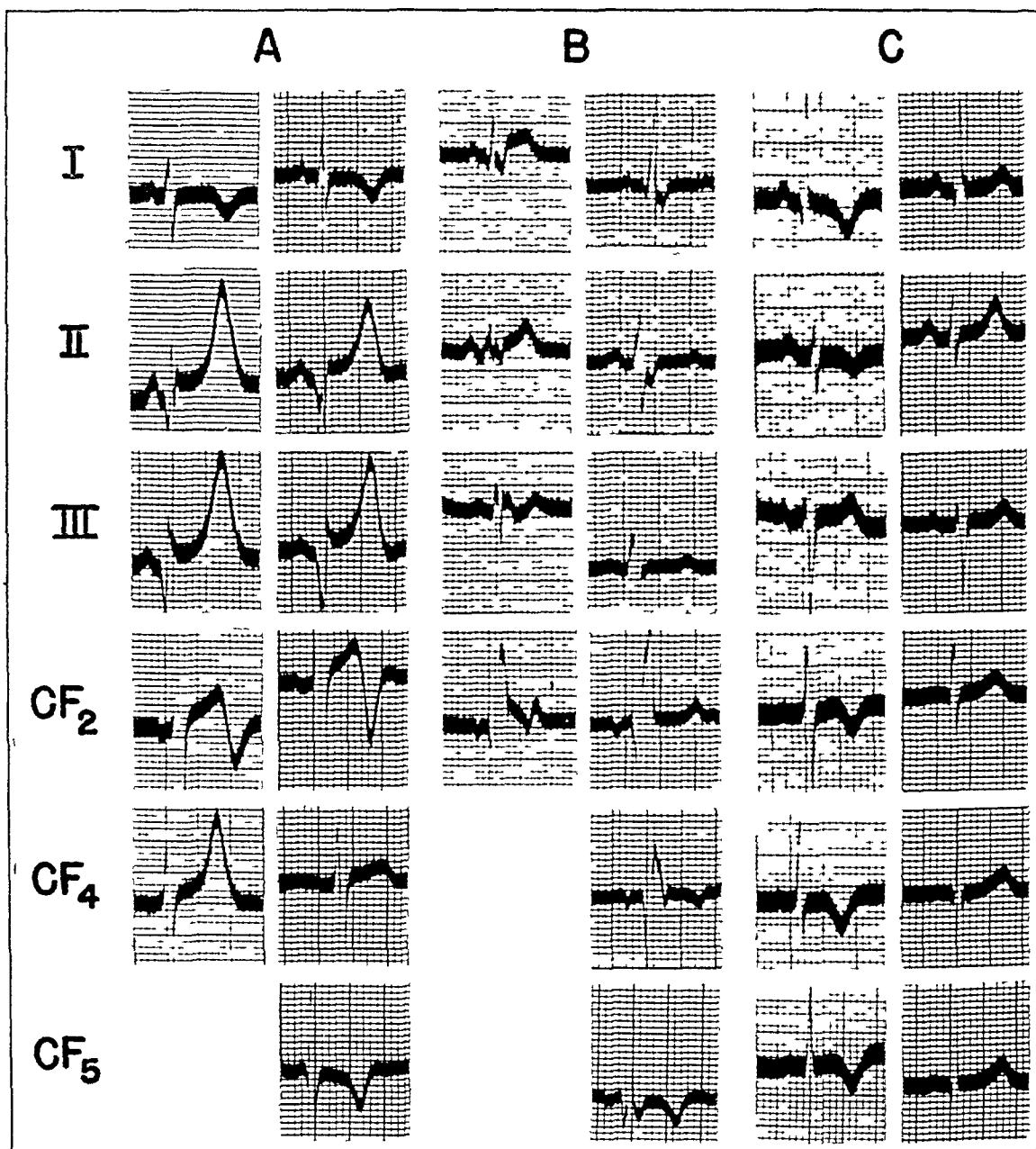
3 Cooksey, W B Coronary Thrombosis Follow-Up Studies with Especial Reference to Prognosis, J A M A **104** 2063 (June 8) 1935

4 Master, A M, and Dack, S Rehabilitation Following Acute Coronary Artery Occlusion, J A M A **115** 828 (Sept 7) 1940

5 (a) King, H C Prognosis in Coronary Heart Disease and After Coronary Occlusion, Ohio State M J **33** 524, 1937 (b) Master, A M, Jaffe, H L, and Dack, S The Treatment and Immediate Prognosis of Coronary Artery Thrombosis, Am Heart J **12** 549, 1936 (c) Conner, L A, and Holt, E The Subsequent Course and Prognosis in Coronary Thrombosis—an Analysis of Two Hundred and Eighty-Seven Cases, *ibid* **5** 705, 1930

6 Katz, L N Electrocardiography Including an Atlas of Electrocardiograms, ed 2, Philadelphia, Lea & Febiger, 1946

showed no evidence of hypertension, angina or heart failure. Angina pectoris and hypertension appeared alone in 3 cases each, and in combination in 3 cases. One patient suffered from angina and heart failure. None of the patients in this group had heart failure at the time of admission.



A, electrocardiogram of a white man of 33. The first record was taken on June 2, 1941, ten days after the clinical episode. The follow-up record was taken on March 13, 1947. There is little restitution. *B*, a white man of 60. The first record was taken on March 7, 1940, one day after the clinical episode. The follow-up record was taken on March 5, 1947. There is partial restitution. Evidence of the healed infarct is shown by the deep Q wave in CF_2 and CF_4 . *C*, a white woman of 68. The first record was taken on October 8, 1943, two weeks after the clinical episode. The follow-up record was taken on March 13, 1947. There is complete restitution.

3 *Complete Electrocardiographic Restitution*—Only 9 of the 100 patients examined had complete electrocardiographic restitution. Eight were males. Four of these had no hypertension, angina or heart failure, and 4 had clinical hypertension only. The remaining patient had angina pectoris. None of this group had heart failure on admission.

Because the number of patients with partial and complete restitution was small it would not be warranted to draw a statistical correlation. However, in the two groups together there were 23 patients, and of these 8, or 35 per cent, had no hypertension, angina or heart failure at follow-up. This figure is comparable to that for the group with little restitution, in which 24 of 77 patients (31 per cent) had no sequelae. Our breakdown indicates that hypertension and angina pectoris are

Distribution of the 100 Patients at the Time of Follow-Up

	No Angina, Hyper tension or Failure	Angina Alone	Hyper tension Alone	Failure Alone	Angina, Hyper tension and Failure	Angina and Hyper tension	Hyper tension and Failure	Angina and Failure	Totals
Little electrocardiographic restitution									
Males	19	9	14	0	2	10	2	3	59
Females	5	2	2	1	1	5	2	0	18
Totals	24 (31.2%)	11 (14.3%)	16 (20.8%)	1 (1.3%)	3 (3.9%)	15 (19.4%)	4 (5.2%)	3 (3.9%)	77
Partial electrocardiographic restitution									
Males	4	2	0	0	0	2	0	1	9
Females	0	1	3	0	0	1	0	0	5
Totals	4 (28.7%)	3 (21.4%)	3 (21.4%)	0	0	3 (21.4%)	0	1 (7.1%)	14
Complete electrocardiographic restitution									
Males	4	1	3	0	0	0	0	0	8
Females	0	0	1	0	0	0	0	0	1
Totals	4 (44.4%)	1 (11.1%)	4 (44.4%)	0	0	0	0	0	9
Totals	32	15	23	1	3	18	4	4	100

most frequently noted clinically in the follow-up examination of the patient with myocardial infarction.

There was little difference in the rate of occurrence of angina among patients with little, partial or complete restitution. In general, the distribution of angina and hypertension, alone or in combination, was about the same in the three groups classified according to degree of electrocardiographic restitution. Heart failure, alone or in combination with angina and/or hypertension, was limited almost entirely (in 11 of 12 cases) to the group with little restitution.

HYPERTENSION

Forty-eight patients had hypertension alone or in combination with heart failure and/or angina, of these, 15 were females and 33 males (a somewhat higher ratio of females to males than in the total group).

studied) In the cases of those patients whose blood pressure levels previous to infarction were known, the trend was toward a higher blood pressure level at the time of the follow-up Master and his associates⁷ reported a return of hypertension in two thirds of their cases Chambers⁸ pointed out that 58 per cent of his patients regained the hypertension by the end of the second year and that in those cases in which the blood pressure had not returned to hypertensive levels by the end of the first year there was a greater variety of complaints In our experience, all the patients who had hypertension at follow-up one year or more after infarction had a history of hypertension before infarction, and of these 18 had coexisting angina pectoris

Of the patients in the 23 cases of uncomplicated hypertension, 12 had the pattern of an infarct of the posterior wall, 8, that of an infarct of the anterior wall, 1, that of an infarct of the lateral wall, and 2 that of an atypical infarct Sixteen of these patients had no defect of impulse initiation or conduction and no low voltage in the follow-up electrocardiogram There were 4 instances of conduction disturbances, all were in cases of intraventricular block Disturbances of impulse initiation were seen in 3 cases in which the patients had ventricular premature systoles, and in a fourth in which the patient had nodal premature systoles together with intraventricular block

ANGINA PECTORIS

Fifteen patients, 12 of whom were males, had only angina pectoris at follow-up Angina occurred alone with almost the same frequency in patients who had anterior wall infarct patterns or posterior wall infarct patterns, viz, in 4 of the former and 5 of the latter Angina occurred in 3 cases in which patients showed lateral wall infarct patterns and in 3 cases in which the pattern was atypical Of these 15 patients who had angina without hypertension or heart failure, 11 showed little electrocardiographic restitution, 3 partial restitution and 1 complete restitution Therefore, there is no actual relationship between the various types of electrocardiographic restitution and the clinical syndrome of angina pectoris It appears in patients with complete restitution as well as in those with partial or little restitution

Considering all 39 cases of anginal syndrome in the groups with little and partial restitution (which included 91 cases), an interesting fact appeared These groups were those in which the electrocardiographic diagnosis was chronic coronary insufficiency Thus, more than

7 Master, A M, Jaffe, H L, Dack, S, and Silver, N The Course of the Blood Pressure Before, During and After Coronary Occlusion, *Am Heart J* 26 92, 1943

8 Chambers, W N Blood Pressure Studies in One Hundred Cases of Coronary Occlusion with Myocardial Infarction, *Am J M Sc* 213 1, 1947

1 in 3 of our patients with the electrocardiographic pattern of chronic coronary insufficiency had a clinical syndrome of angina

There were 11 patients in this group who had no disturbance of impulse origin or conduction. Three patients had intraventricular block, associated in 1 case with auricular premature systoles and in 1 with ventricular premature systoles. One patient had auricular premature systoles alone. Low voltage was observed once.

HEART FAILURE

Heart failure alone was observed only once at follow-up, but it was present 11 times in association with hypertension, angina or both. It occurred with almost the same frequency in association with angina pectoris as with hypertension. The 1 occurrence of isolated heart failure was in a female patient. Although the presence of heart failure is a grave sign, the degree of failure present was minimal except in 1 instance. This patient, who had moderately severe failure, was not receiving digitalis, the blood pressure was 300 systolic and 110 diastolic, and the electrocardiogram was grossly abnormal. Except in 1 instance, all the patients with heart failure showed little electrocardiographic restitution. The 1 patient had angina, associated with heart failure and with partial electrocardiographic restitution.

It should be pointed out that digitalization is indicated when the patient has had an infarct and survives, and when heart failure develops for reasons other than that of a new infarct. Even when heart failure is due to a new infarct adequate digitalization is not contraindicated and is without hazard when properly employed.

Heart failure was observed in the cases of 5 patients with previous posterior wall infarct patterns, in those of 2 patients with anterior wall infarct patterns, in those of 2 patients with lateral wall infarct patterns and in those of 3 patients with atypical patterns. The electrocardiogram of 1 patient, who was in congestive heart failure without angina or hypertension, showed low voltage. This was the only defect in impulse initiation or conduction noted in cases in which patients had heart failure. Such abnormalities of impulse initiation as ventricular, nodal and auricular premature systoles represent a potential hazard since more serious ectopic rhythms, such as auricular fibrillation, ventricular tachycardia or ventricular fibrillation, may develop later, with the hazard in the case of the latter two of unexpected death. Patients with the latter conditions should receive quinidine.

COMBINATION OF HYPERTENSION, ANGINA PECTORIS AND HEART FAILURE

In our series, 20 males and 9 females had some combination of angina, failure and/or hypertension. Angina and hypertension was the most frequent combination, it occurred in 18 cases, in 15 of which

patients had little electrocardiographic restitution. None of the patients with complete electrocardiographic restitution had combinations of these conditions, however, it must be remembered that there were only 9 patients in that group.

Of the 29 patients with more than one clinical condition at follow-up, at the time of infarction 8 had anterior wall infarct patterns, 11 posterior wall infarct patterns, 7 lateral wall infarct patterns and 3 atypical infarct patterns. Two of the patients had intraventricular block, which in 1 instance occurred with auriculoventricular block. One patient who had ventricular premature systoles also had auricular fibrillation. The fibrillation and an atypical infarct pattern were present at the time of hospitalization, and at follow-up there was little electrocardiographic restitution. One other instance of auricular fibrillation was noted, this, too, was in a case with little restitution. Low voltage was observed in 2 instances. Twenty-one patients had no defects of impulse initiation or conduction. Their tracings were all consistent with the electrocardiographic diagnosis of chronic coronary insufficiency.

ABSENCE OF HYPERTENSION, ANGINA PECTORIS AND HEART FAILURE

Thirty-two patients (27 males and 5 females) were found to have no angina, heart failure or hypertension at follow-up. Most of these patients had either anterior wall infarct patterns (18 patients) or posterior wall infarct patterns (12 patients). Disturbances of impulse initiation and conduction occurred with almost the same frequency in this group as in the group with hypertension alone. There were 3 instances of intraventricular block, 1 associated with auriculoventricular block and 1 with ventricular premature systoles. In 2 instances, the electrocardiogram showed little restitution, 1 patient had intraventricular block alone, and 1 had both intraventricular and auriculoventricular block. Conduction disturbances, all ventricular premature systoles, occurred in 3 cases. Low voltage was observed 4 times as an isolated disturbance. Twenty-two patients had defects of impulse initiation or conduction.

COMMENT

It is of considerable interest and importance that of 100 patients examined one to six years after infarction, 77 had little electrocardiographic restitution and only 9 had complete restitution. It is evident that the electrocardiographic pattern can prognosticate neither survival nor rehabilitation, for the greatest percentage of surviving patients had the most abnormal records and all the patients had resumed their previous occupations. Physicians must be cognizant of the large number of patients whose electrocardiograms made after infarction will show little change in contour from the pattern of recent infarction over a period of years. The cause of episodes of precordial pain in these

patients may be misdiagnosed as recent infarction on the basis of the electrocardiogram unless serial records are made. Comparison of the frequency of clinical angina pectoris with the large number of tracings which indicate the electrocardiographic diagnosis of chronic coronary insufficiency demonstrates the correlation between these two distinct entities in patients surviving infarction.

The clinical state of the patient can be anticipated in some respects with the aid of the electrocardiogram. Among our 100 patients, the number without hypertension, angina pectoris or heart failure was about equal in the two groups of those with little electrocardiographic restitution and those with partial and complete restitution. Angina pectoris and hypertension, singly or in combination, occurred without statistical differences in the three groups classified according to electrocardiographic restitution. Heart failure was the only entity which was heavily concentrated in one group. Alone, or in combination with angina pectoris and hypertension, it was present in 11 patients with little restitution and only once in the group showing partial restitution. Heart failure associated with acute myocardial infarction enhances the gravity of the prognosis.² Only 3 of our 100 patients exhibited heart failure on admission. The fact that 11 patients with heart failure on follow-up were in the group with little restitution would indicate that in this one respect the electrocardiogram which changes little after acute infarction carries with it special importance. For this reason it is justifiable to be more optimistic when there is complete electrocardiographic restitution after infarction. The occurrence of clinical angina in 39 patients of 91 whose condition was electrocardiographically diagnosed as chronic coronary insufficiency (little or partial restitution) indicates the frequency of the association of clinical angina with the electrocardiographic pattern of chronic coronary insufficiency in patients surviving myocardial infarction.

SUMMARY AND CONCLUSIONS

One hundred patients were examined who had survived one to six years after acute myocardial infarction.

The electrocardiograms of 77 of these 100 patients showed little restitution, those of 14 showed partial restitution and those of 9 showed complete restitution.

The electrocardiographic pattern after infarction did not prognosticate survival of the patient.

Heart failure appeared almost entirely in the group of patients with little electrocardiographic restitution.

The electrocardiographic diagnosis of chronic coronary insufficiency is distinct from the clinical syndrome of angina, yet, clinical angina occurred in 43 per cent of patients surviving infarction whose electrocardiographic pattern was that of chronic coronary insufficiency.

INTRAVENOUS CATHETERIZATION OF THE HEART IN SUSPECTED CONGENITAL HEART DISEASE

Report of Seventy-Two Cases *

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RECENT advances in the surgical alteration¹ and correction of certain congenital defects of the heart and the great vessels make it imperative that more exact diagnoses of such lesions be made. Intravenous catheterization of the heart has been found to be a most useful aid in ascertaining the condition when such congenital abnormalities are suspected. Forssmann,² in 1929, first introduced the method by catheterizing his own heart. In 1941, Cournand and Ranges³ emphasized its applicability to the study of certain physiologic changes that occur in various types of heart disease. Blood samples may be obtained from various parts of the venous system, from the right side of the heart and from the pulmonary artery and its branches for estima-

* Reports of 23 of the cases were used in a preliminary report.

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1 (a) Gross, R E, and Hubbard, J P. Surgical Ligation of a Patent Ductus Arteriosus. Report of First Successful Case, *J A M A* **112** 729 (Feb 25) 1939. (b) Blalock, A, and Taussig, H B. Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, *ibid* **128** 189 (May 19) 1945. (c) Crafoord, C, and Nylin, S. Congenital Coarctation of the Aorta and Its Surgical Treatment, *J Thoracic Surg* **14** 347, 1945. (d) Gross, R E, and Hufnagel, C A. Coarctation of the Aorta. Experimental Studies Regarding Its Surgical Correction, *New England J Med* **233** 287, 1945.

2 Forssmann, W. Die Sondierung des rechten Herzens, *Klin Wchnschr* **8** 2085, 1929.

3 Cournand, A, and Ranges, H A. Catheterization of Right Auricle, *Proc Soc Exper Biol & Med* **46** 462, 1941.

tion of the oxygen content. At the same sites, the blood pressure may be determined with a Hamilton manometer⁴ or similar apparatus. Other investigators⁵ have used this method to study the hemodynamics in various derangements of the cardiorespiratory system. The purpose of the present paper is to present the results of intravenous catheterization of the heart in 72 cases of suspected congenital heart disease.

The normal variation of the oxygen content in the various chambers of the heart has been established by Dexter and others⁶. The normal variation between the superior vena cava and the right atrium auricle is 1.9 volumes per cent, between the right atrium and the right ventricle, 0.9 volumes per cent, between the right ventricle and the pulmonary artery, 0.5 volumes per cent, and within the pulmonary branches themselves, 0.4 volumes per cent.

The technic as described by Cournand⁷ and his group of workers has been used by us with certain modifications to meet specific problems. We administer penicillin prophylactically for twelve hours before the procedure, and a sufficient dose of barbiturates for adequate sedation of the patient is given one to two hours before the examination. An antecubital vein is exposed with aseptic technic, and a small incision is made in its wall. A special radiopaque ureteral catheter (no. 6 F or 9 F) with a curved tip and with a hole in its end is introduced into the vein and passed through the subclavian vein, the superior vena cava, the right atrium and the right ventricle and into the pulmonary artery and its branches whenever possible (fig. 1). In some instances, the catheter may pass into an anomalous pulmonary vein emptying into

4 Hamilton, W. F., Brewer, G., and Brotman, I. Pressure Pulse Contours in the Intact Animal. I. Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, *Am J Physiol* **107**: 427, 1934.

5 Warren, J. V., Brannon, E. S., Stead, E. A., Jr., and Merrill, A. J. The Effect of Venesection and the Pooling of Blood in Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observation in Acute Circulatory Collapse in Three Instances, *J Clin Investigation* **24**: 337, 1945. Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr. The Cardiac Output in Patients with Chronic Anemia as Measured by the Technique of Right Atrial Catheterization, *ibid* **24**: 332, 1945. Brannon, E. S., Stead, E. A., Jr., Warren, J. V., and Merrill, A. J. Hemodynamics of Acute Hemorrhage in Man, *Am Heart J* **31**: 407, 1946.

6 Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sagerson, R. P., and Evans, J. M. Studies of Congenital Heart Disease. II. The Pressure and Oxygen Content of Blood in the Right Auricle, Right Ventricle, and Pulmonary Artery in Control Patients, with Observations on the Oxygen Saturation and Source of Pulmonary "Capillary" Blood, *J Clin Investigation* **36**: 554, 1947. ✓

7 Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF., and Richards, D. W., Jr. Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, *J Clin Investigation* **24**: 106, 1945.

the right atrium through a septal defect, into the left side of the heart and, possibly, into the pulmonary veins or into the aorta. The catheter is under fluoroscopic guidance at all times.

Throughout the procedure, an extremely slow drip of isotonic sodium chloride solution containing heparin sodium is maintained through the catheter to prevent clotting of the blood in the lumen. After the tip



Fig 1—Positions of tip of catheter: 1, superior vena cava, 2, inferior vena cava, 3, right atrium, 4, right atrium, 5, right ventricle, 6, right ventricle, 7, right ventricle near pulmonary conus, 8, proximal portion of right pulmonary artery, 9, right pulmonary artery, 10, left pulmonary artery, 11, left pulmonary artery, and 12, distal portion of left pulmonary artery.

of the catheter has reached the desired spot, several cubic centimeters of blood is withdrawn through the catheter and discarded to avoid any dilution with the sodium chloride solution. Samples of blood are then withdrawn into oiled syringes and stored under oil in iced containers. They are analyzed for oxygen and carbon dioxide content by

the manometric method of Van Slyke and Cullen⁸ Samples are drawn from all the aforementioned areas whenever possible Roentgenograms are obtained to establish each position of the catheter Pressures are recorded by connecting the catheter to a Hamilton optic manometer The patients are given penicillin for forty-eight hours after the procedure

REPORT OF CASES

To date 72 cases have been studied by this procedure The following is a summary of the resulting diagnoses

Acyanotic conditions

Coarctation of the aorta, 3 cases (1 complicated with a patent ductus arteriosus)

Essential (idiopathic) pulmonary hypertension, 2 cases

Potentially cyanotic conditions

Interatrial septal defect, 8 cases

Interventricular septal defect, 15 cases

Uncomplicated, 13 cases

Interventricular septal defect, common truncus arteriosus and pulmonary arteriovenous aneurysm, 1 case

Interventricular septal defect and an associated patent ductus arteriosus, 1 case, operation performed

Interventricular septal defect with right arched aorta, 1 case

Patent ductus arteriosus, 22 cases, diagnosis confirmed in the 18 cases in which operation has been performed to date

Cyanotic conditions

Tetralogy of Fallot, 5 cases, diagnosis confirmed at operation

Tetralogy of Fallot with patent ductus arteriosus, 1 case, operation not performed

Common atrium with possible tricuspid atresia, 1 case

Special conditions

Dilated pulmonary artery with hypoplastic aorta, 1 case

Pulmonary arteriovenous aneurysm, 1 case, findings at catheterization normal

Normal heart, 9 cases, congenital heart disease suspected, normal pressures and gas values observed on catheterization

Diagnosis impossible because of insufficient data, 3 cases

A few of our cases are presented in more detail with comments to illustrate some of the special features one may encounter

Acyanotic Conditions—Coarctation of the Aorta Two patients with uncomplicated coarctation of the aorta, the diagnosis in both cases having been proved at operation, were catheterized In neither case was there significant alteration of

⁸ Peters, J P, and Van Slyke, D D Methods, in Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol 2

the oxygen content or of pressures. The coarcted site, in cases of this type, may be studied roentgenographically by the injection of a 70 per cent solution of iodopyracet injection (diodrast®) through a catheter introduced into the proximal portion of the aorta via the carotid or brachial arteries.

Catheterization in a third case, in which a combination of patent ductus arteriosus and coarctation of the aorta existed, yielded the following data:

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	12.5	
Right atrium	12.74	0/—3
Right ventricle	12.25	90/2
Right pulmonary artery	18.30	68/70

Idiopathic Pulmonary Hypertension. S. D., a girl of 4, was admitted to the hospital for evaluation of a heart murmur which had been known to be present since she was 7 months old. She had not been born a blue baby and had had no episodes of cyanosis. She had shown no limitation of her physical or mental development and was able to keep up with her own age group in participation in games.

Physical examination showed a slender, well developed, acyanotic girl with ptosis of the left eyelid. There was no clubbing. The blood pressure was 125 systolic and 75 diastolic. Examination of the heart revealed a somewhat over-accessible right ventricle and some enlargement of the left side of the chest anteriorly. The left border of the heart was at the anterior axillary line. There was a sinus rhythm, the rate being 96 beats per minute. A harsh, grade 5 systolic murmur was heard over the entire precordium, the maximum intensity being in the second left interspace. No diastolic murmur was heard. Electrocardiograms revealed right axis deviation. Roentgenograms showed evidence of enlargement of the right atrium and the inflow tract of the right ventricle.

Venous catheterization studies revealed essentially the same oxygen content (13.3 volumes per cent) in the superior vena cava, the right atrium, the right ventricle and the main and right pulmonary arteries. The blood pressure in the right atrium was normal, but in the right ventricle readings of 86 systolic and 40 diastolic and 86 systolic and 60 diastolic were made, and in the pulmonary artery 112 systolic and 60 diastolic and 98 systolic and 62 diastolic.

A diagnosis of idiopathic pulmonary hypertension was made. No evidence of a left to right shunt was noted. No operation was performed.

A similar case of pronounced increase in pressure in the right ventricle and the pulmonary artery pressure was in an acyanotic child with a systolic murmur. This patient, likewise, showed no evidence of left to right shunt. The cause of the increased pulmonary hypertension was not obvious on either physical or roentgen examination.

Potentially Cyanotic Conditions—Interatrial Septal Defect. S. A. was a white woman of 24 who had been told early in life that she had a heart murmur. For the past year she had been experiencing increasing tiredness, and for the past six months exertional dyspnea had developed, but on no occasion had she noted cyanosis. There had been no swelling of the ankles or nocturnal dyspnea. There was a loud, harsh systolic murmur, heard over the entire precordium but with its loudest intensity in the second left interspace at the parasternal line. It was accompanied with a palpable thrill. The systolic arterial pressure was 120 and the diastolic pressure was 75. There was no stunting of growth, no cyanosis or clubbing and no evidence of decompensation. Roentgenograms revealed a sug-

gestion of anterior bulging of the heart in the left anterior oblique position and some enlargement of the right heart in posterior-anterior films. The pulmonary artery appeared somewhat dilated, and there was a suggestion of a "hilar dance" on fluoroscopic examination. Right axis deviation was noted on the electrocardiographic tracing.

Catheterization studies of the heart in this case yielded the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %
Superior vena cava	10.9	34.5
Inferior vena cava	10.4	34.2
Right atrium	13.7	26.0
Right ventricle	13.8	26.6
Right pulmonary artery	13.6	26.4

D. L., a schoolboy of 7, was referred for study after the detection of a heart murmur by the school physician. The patient had always been under average size, but alert and active. The mother denied that the child was ever cyanotic or dyspneic, he ran as long and as fast as his friends.

Physical examination showed an undernourished, undersized, active boy. The blood pressure in both arms was 100 systolic and 65 diastolic, after exercise it was 100 systolic and 30 diastolic. A slight prominence of the left side of the thorax was noted. The left border of cardiac dulness was within normal limits. A blowing systolic murmur was heard loudest in the first and second interspaces between the sternum and the midclavicular line and was well transmitted over the entire precordium to the axillas and over the shoulder strap areas to the intra-scapular area. The second pulmonic sound was slightly accentuated. There was no cyanosis or clubbing. A fluoroscopic examination showed moderate prominence of the pulmonary artery and a suggestion of a "hilar dance." The electrocardiogram revealed right axis deviation.

Heart catheterization studies in this case revealed an increase of oxygen of 4.9 volumes per cent from the superior vena cava to the right atrium. The blood pressures were recorded as 5 systolic and 2 diastolic in the right atrium, 34 systolic and 5 diastolic in the right ventricle and 34 systolic and 5 diastolic in the right pulmonary artery.

Atrial septal defects can usually be diagnosed by noting the significant increase in the oxygen content of the blood from the right atrium as compared with that of the blood from the venae cavae. This results from the shunting of blood from the left atrium to the right atrium. Unusual defects, such as the draining of the pulmonary vein into the right atrium, may occasionally be encountered. An increase in the oxygen content from the atrium to the pulmonary vein as well as roentgenographic evidence of the position of the catheter (fig. 2) will establish the diagnosis. In this instance, the oxygen content of the right atrium was 13.3 volumes per cent, and that of the pulmonary vein, 21.6 volumes per cent. Brannon, Weens, and Warren⁹ found that a diagnosis of

⁹ Brannon, E. S., Weens, H. S., and Warren, J. R. Atrial Septal Defect—Study of Hemodynamics by the Technique of Right Heart Catheterization, *Am J M Sc* **210** 480, 1945.

interatrial septal defect could be made by introducing the catheter through the septal defect or by observing a significant increase in the oxygen content of the blood in the right atrium as compared with that obtained from the superior vena cava. The former method, however, has been unsuccessful in the majority of cases. Baldwin, Moore and

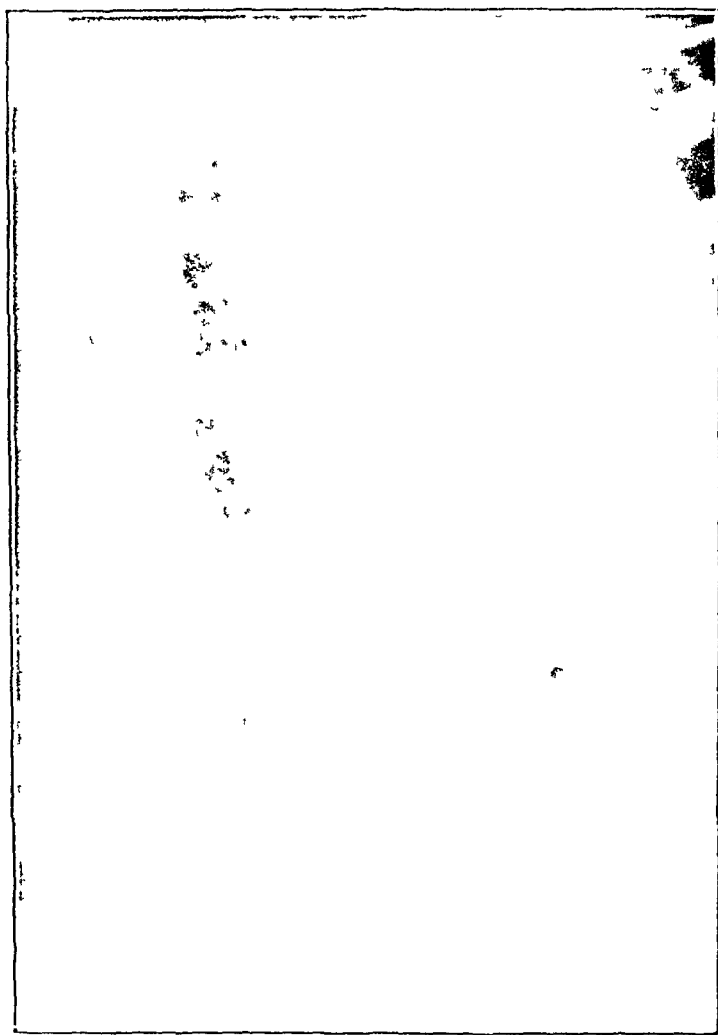


Fig 2—Tip of catheter in a pulmonary vein communicating with the right atrium

Noble¹⁰ observed an instance in which tricuspid insufficiency associated with an interventricular septal defect gave a significant rise in the oxygen content of the right atrium. The authors recognized the disorder by an analysis of the atrial and ventricular pressure tracings,

10 Baldwin, E deF, Moore, L V, and Noble R P. The Demonstration of Ventricular Septal Defect by Means of Right Heart Catheterization, *Am Heart J* 32 152, 1946

as described by Cournand¹¹ Considerable variation in the pressure in the right ventricle has been noted, a low pressure of 23 systolic and 3 diastolic and a high pressure of 87 systolic and 8 diastolic having been recorded in the pulmonary arteries, a low pressure of 20 systolic and 8 diastolic and a high pressure of 87 systolic and 6 diastolic were noted on one occasion

Interventricular Septal Defect—Uncomplicated R B was a boy of 4 whose parents had been told that he had congenital heart disease at the age of 2 months However, the child had continued to develop normally both physically and mentally, and there had been no retardation of his activities He had experienced no dyspnea, cyanosis or periods of syncope

Physical examination showed a slender, alert white boy of 4 There was no evidence of clubbing of the finger nails or cyanosis A systolic thrill was felt in the third left interspace, and a harsh systolic murmur, heard all over the precordium, reached its maximum in the second left interspace There was no cardiac enlargement Roentgenograms revealed no definite cardiac enlargement, and no "hilar dance" was noted on fluoroscopic examination An electrocardiographic tracing was well within normal limits

Catheterization studies revealed the following data

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	12.13	
Right atrium	12.60	2/0
Right ventricle	16.44	77/16
Right pulmonary artery	16.40	
Aorta	18.88	80/52

The catheter was passed through the ventricular septal defect, out through the aorta and into the left subclavian artery (fig 3)

The recognition of an interventricular septal defect by venous catheterization can be made on the observation of a significant increase in the amount of oxygen in the right ventricle as compared with that in the right atrium or on passing the catheter through a septal defect into the left ventricle and out through the aorta Immediately as the catheter enters the systemic side an increase in systolic and diastolic pressure is noted

Associated with Other Defects A significantly elevated oxygen content of the blood in the right ventricle may reflect the presence of an interventricular septal defect or, theoretically, a patent ductus with associated incompetency of the pulmonic valve Three instances of the latter phenomenon were suspected by Dexter and his associates¹² In 1 of their cases, after surgical intervention which eradicated all

11 Cournand, A, Lauson, H D, Bloomfield, R A, Breed, E S, and Baldwin, E deF Recording of Right Heart Pressures in Man, *Proc Soc Exper Biol & Med* 55 34, 1944

12 Dexter, L, Haynes, F W, Burwell, C S, Eppinger, E C, Sosman, M C, and Evans, J M Studies of Congenital Heart Disease III Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy, Ventricular Septal Defect, and Auricular Septal Defect, *J Clin Investigation* 26 561, 1947

murmurs, venous catheterization failed to reveal any significant variation of oxygen content in the right atrium, the right ventricle or the pulmonary artery. They stated the belief that a diagnosis of interventricular septal defect in the presence of a patent ductus should be made with caution.

Associated with Common Truncus Arteriosus and Pulmonary Arteriovenous Aneurysm. C. A. D.'s parents had been told that the child had a heart murmur

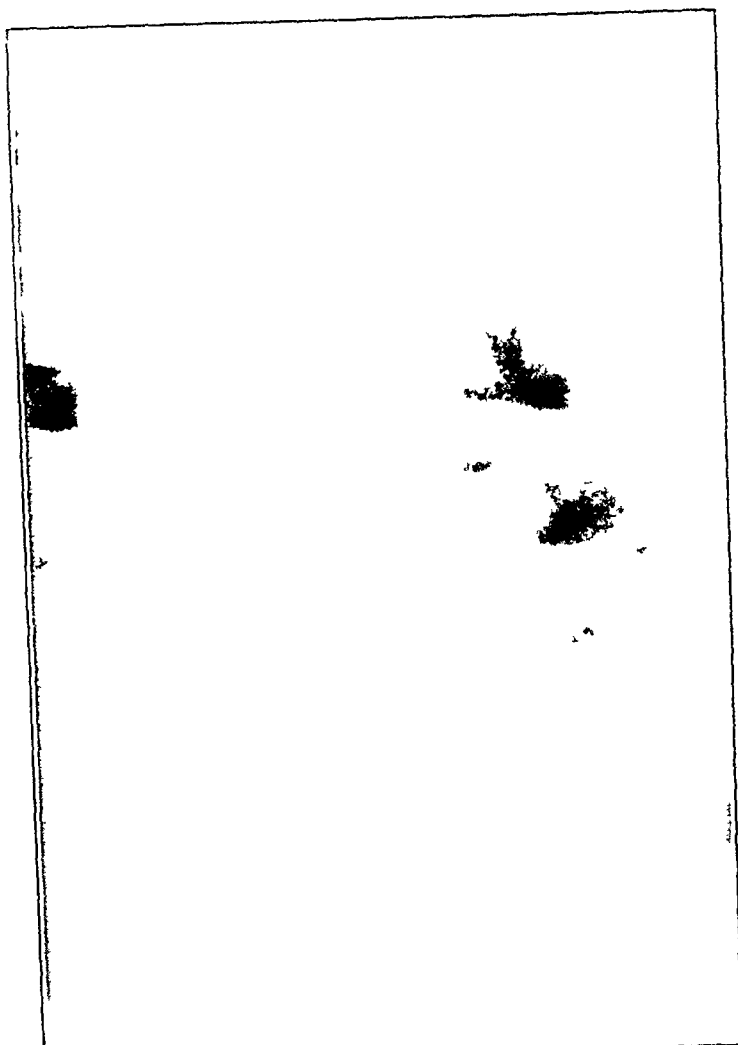


Fig. 3—Tip of catheter in the left subclavian artery, having passed through a ventricular septal defect.

at 5 months. The mother had had German measles when she was six weeks pregnant. The child had been slow to develop both physically and mentally and recently had been found to have bilateral eighth nerve deafness. There had been no definite episodes of cyanosis. Physical examination showed a small, undernourished child. The left border of the heart was at the anterior axillary line. A harsh, systolic murmur with its maximum intensity in the first and second left interspaces was heard over the entire precordium, it was transmitted to the left side and to the back. There was a late systolic accentuation with a

short diastolic component. Fluoroscopic examination showed a questionable enlargement of the left ventricle and the right atrium. The pulmonary conus was prominent.

Catheterization studies of the heart revealed the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %
Superior vena cava	12.07	34.5
Right atrium	11.84	35.9
Right ventricle	17.03	31.1
Right pulmonary artery	16.27	37.5

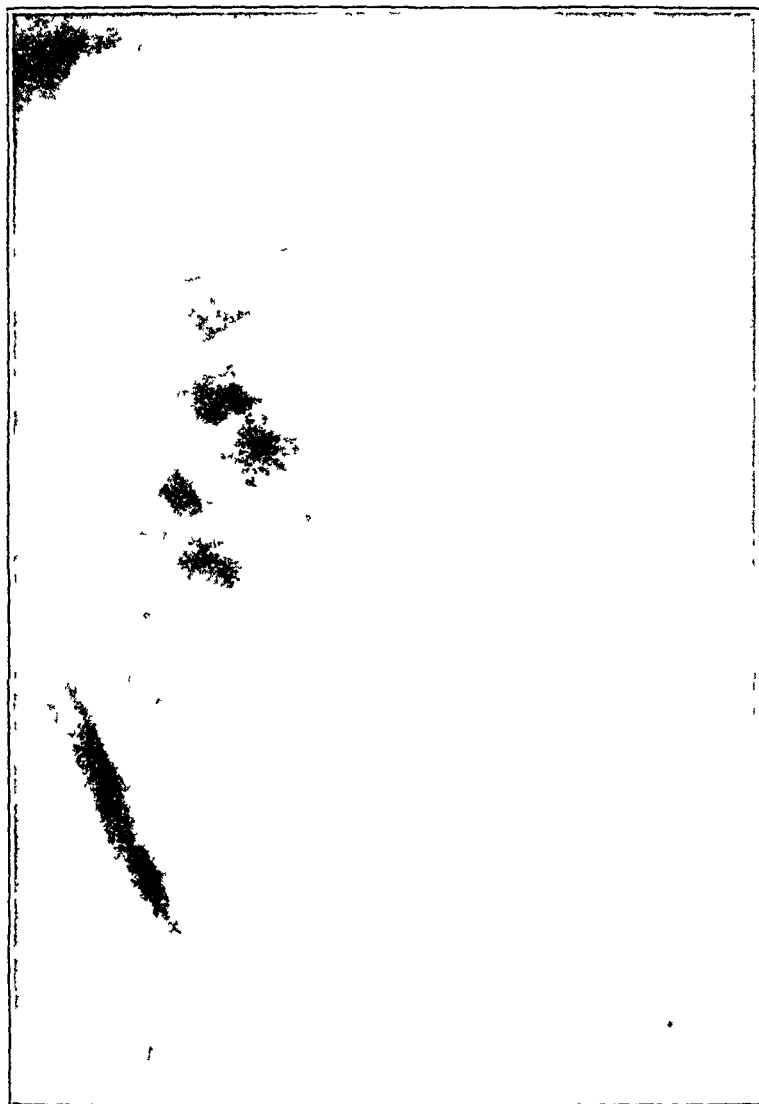


Fig. 4—Tip of catheter in a right-sided aorta, having passed through a ventricular septal defect.

Because the experience of Dexter and his co-workers in the previously mentioned cases, an exploration was thought advisable even though catheterization had showed only an interventricular septal defect. At operation, the cause of the to-and-fro murmur was found to be a pulmonary arteriovenous fistula at the interlobar fissure on the left side. Also present was a common truncus arteriosus, the left pulmonary artery arose from it, and the right pulmonary artery arose from the left pulmonary artery.

Associated with Patent Ductus Arteriosus J. P., a housewife of 21 who had had a heart murmur since infancy, came to the hospital for evaluation of the murmur.

She had never had dyspnea, cyanosis or other symptoms referable to the heart. The systolic arterial pressure was 125, and the diastolic pressure was 80. The heart was enlarged to the left midaxillary line, and a thrill was felt over the precordium. A grade 4 to-and-fro machinery murmur was present in the pulmonic area. Roentgenograms revealed severe cardiac enlargement and a pulmonary "hilar dance." A left ventricle hypertrophy pattern was noted on the electrocardiographic tracing. The catheter was passed into the superior vena cava, the right atrium, the right ventricle and the pulmonary artery. The catheter was then withdrawn into the right ventricle and passed through a ventricular septal defect into the aorta and the left carotid and subclavian arteries. An estimate of the oxygen content in the various sites showed 12.31 volumes per cent in the right atrium, 18.04 volumes per cent in the right ventricle and 18.17 volumes per cent in the pulmonary artery.

Patent ductus arteriosus was diagnosed because of the typical murmur and interventricular septal defect because of the differential in oxygen content and the passing of the catheter through the defect. At operation, a patent ductus arteriosus was found and ligated. After operation, a grade 2 systolic murmur persisted in the third and fourth left interspaces in the parasternal line. The to-and-fro murmur was gone.

Over a five month postoperative observation period, there was a pronounced decrease in cardiac size and an abolition of the pulmonary hilar dance.

Associated with Right-Arched Aorta. Y. B., a girl of 2, was studied because of tachycardia, underweight and a heart murmur. She had been cyanotic once or twice hours when, at the age of 1 year, she had chickenpox with otitis media. There was no clubbing. The heart was slightly enlarged to the left. A loud, harsh systolic murmur was heard in the third left interspace parasternally. The catheter could not be passed into the pulmonary artery but was passed from the right ventricle into the left ventricle and into a right arched aorta (fig. 4).

Catheterization studies of the heart revealed the following data:

Site	Oxygen, Volumes %	Blood Pressure
Right atrium	14.65	25.30/15.20
Right ventricle	13.71	75.80/40.50
Aorta	17.80	100.112/70.80

The diagnosis was interventricular septal defect and right arched aorta.

Patent Ductus Arteriosus. P. L., a white boy of 4, had developed slowly, not walking until the age of 22 months. His mother remarked that he would always "take it slow, like an old man." Physical examination showed a small, underdeveloped child weighing 35 pounds (15.9 Kg.). There was no clubbing or cyanosis. The left side of the chest was prominent. Over the base of the heart, a systolic thrill could be palpated. There was a harsh, grade 4 systolic murmur in the second and third left interspaces, transmitted to the left side. At the fourth left interspace, there was a questionable diastolic component. However the phonocardiogram clearly indicated the diastolic murmur (fig. 5). The second pulmonic sound was accentuated. The electrocardiogram was normal. Fluoroscopic examination showed an enlarged cardiac shadow and a "hilar dance." Previously, the diagnosis had always been that of an interatrial septal defect because of the absence of a typical machinery murmur. However, catheterization studies revealed the oxygen content of the blood to be 10.8 volumes per cent in the superior vena cava, 10.4 volumes per cent in the right atrium, 10.3 volumes per cent in the right ventricle, 12.6 volumes per cent in the right pulmonary artery and 13.6 volumes per cent at the bifurcation of the pulmonary artery. The patient subsequently had a large patent ductus ligated.

The condition of the patient had been misdiagnosed because the diastolic component of the murmur was not easily elicited. The case illustrates the value of stethocardiography and cardiac catheterization. The child was seen for a follow-up period of several months. All murmurs had disappeared, and, for the first time, he was gaining weight. His activity had increased greatly.

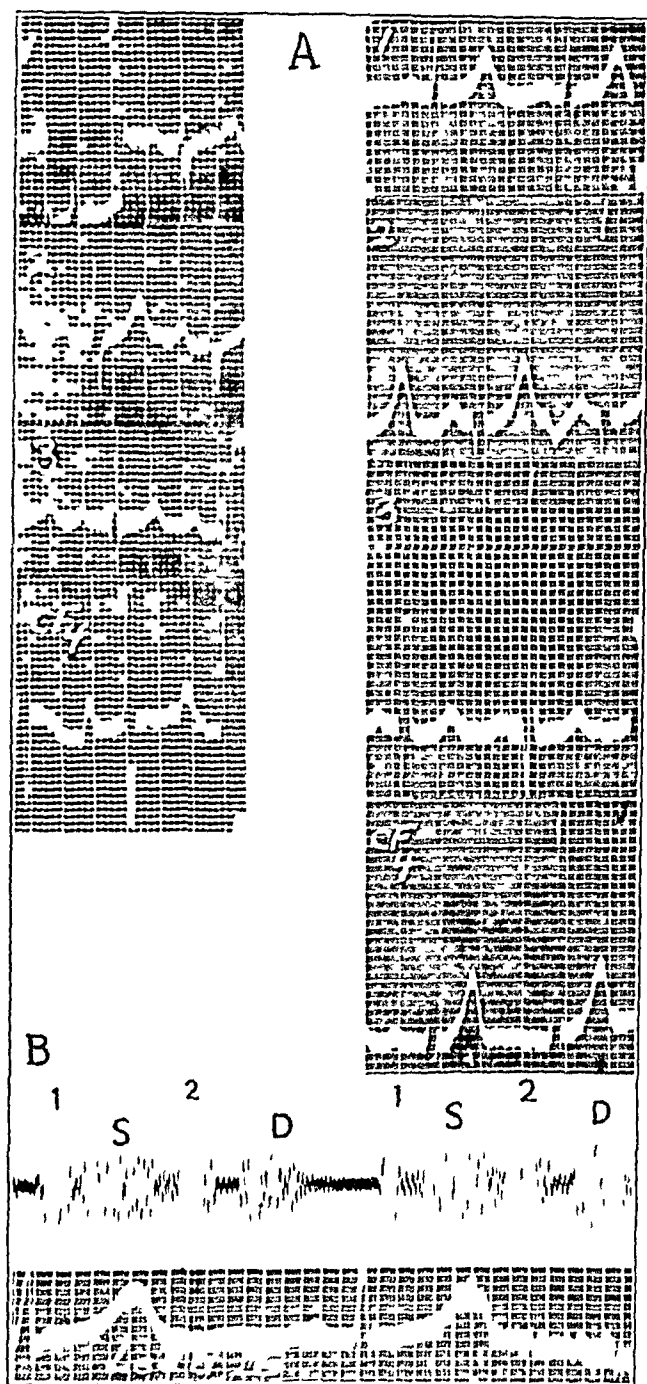


Fig 5—A, electrocardiographic tracing recorded in standard leads I, II, III and CF₄ in cases of patent ductus arteriosus. B, phonocardiogram recorded in the pulmonary region revealing the presence of a systolic and a diastolic murmur, although auscultation revealed only a systolic murmur. Photographs from Brooke General Hospital, United States Army.

J M, a white boy of 22 months, had been delivered normally, weighing 7½ pounds (3.5 Kg). A "heart murmur" was discovered at the age of 2 months. The child had had frequent infections of the upper respiratory tract, lasting two

to three weeks and accompanied with temperatures as high as 103 to 105 F for one or two days. There had been no cyanosis. Physical examination showed a small white boy, weighing 22½ pounds (10.2 Kg). The left side of the chest was more prominent than the right, and there were pronounced visible pulsations over the left side of the precordium. The heart was enlarged to percussion both to the right and to the left. A palpable, pronounced systolic thrill was present over the left side of the precordium. A harsh, grade 5 systolic murmur and a high-pitched grade 3 diastolic murmur were best heard over the second and third left interspaces and were transmitted to the apex. A questionable presystolic murmur was present at the apex. Fluoroscopic examination showed enlargement of the left and right ventricles. The pulmonary area pulsated actively. The stream of barium sulfate was deviated in the region of the left atrium. The electrocardiogram showed a first degree heart block, a rate of 90 beats per minute and a P-R interval of 0.22 second. The QRS interval in leads I and II was diphasic. The diagnosis of patent ductus arteriosus and possible rheumatic heart disease was made at that time. The child was followed closely, the condition did not improve. It was believed that the cardiomegaly was increasing. Because of the uncertain diagnosis it was decided to catheterize the boy.

The oxygen content values were as follows: superior vena cava, 87 volumes per cent, right atrium, 86 volumes per cent, right ventricle, 86 volumes per cent, right pulmonary artery, 14.4 volumes per cent, and left pulmonary artery, 18.8 volumes per cent. The patient was operated on, and a large ductus was ligated. When the patient was seen three months later, the change was remarkable. The chest wall was quiet, the thrill was not felt and all murmurs had disappeared. On fluoroscopic examination, the pulsations of the heart were found to be normal. An electrocardiogram still showed first degree heart block. At the time of this report, the patient has gained weight, has been rather active and has had no respiratory infections since his discharge from the hospital. Because of the first degree block rheumatic heart disease could not be excluded from the diagnosis, but the patient apparently had been having most of his difficulty because of a large patent ductus.

J. L., a male physician of 24, was known to have had a heart murmur at least since the age of 6 or 7. He had developed normally and had had no cardiac disorders. Results of the examination were normal except for a grade 2 systolic murmur at the second, third and fourth left interspaces in the parasternal line and at the apex. Fluoroscopic examination of the chest revealed normal conditions, as did the electrocardiograms. A stethogram revealed only a systolic murmur.

Catheterization studies of the heart revealed the following data:

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	14.28	
Right atrium	14.34	8/4
Right ventricle (apex)	14.63	24.30/10.12
Right ventricle (base)	14.58	
Left pulmonary artery	20.30	
(2 samples)	19.84	19/10

A diagnosis of patent ductus arteriosus was made, the operation has not been performed at the time of writing.

The diagnosis of a patent ductus arteriosus is made when a significant increase over that of the right ventricle is noted in the oxygen content of the pulmonary artery. Samples of blood must be taken fairly close to the hilar region in the pulmonary area to avoid getting capillary blood which has already been oxygenated.

In the majority of our cases of patent ductus arteriosus, the pressures in the right ventricle and in the pulmonary artery were within normal limits or only slightly increased. In 4 of the series of cases of patent ductus arteriosus, only systolic murmurs were audible, in 2, there was stethographic evidence of a diastolic component, and in 2 there was not. In 3 of the cases operation was performed, the presence of the ductus was confirmed and the murmur disappeared. An operation has not been performed in the fourth case at the time of writing. In about half the cases there was a significant drop in the systemic diastolic pressure after exercise. In 3, systolic murmurs were found to persist after ligation. Repeated catheterization studies are planned in these cases.

Cyanotic Conditions—Tetralogy of Fallot. Uncomplicated. D. A., a girl of 4½ years had been born a blue baby and at 3 months had had a severe attack of congestion of the lung with severe cyanosis. The patient had persistent mild cyanosis which had been exaggerated by two more episodes of pulmonary congestion. She frequently squatted to get her breath after walking a short distance. She had considerable limitation of her physical activities.

Physical examination showed an undernourished, underdeveloped, cyanotic white girl. Moderate suffusion of the conjunctivas was present. No definite cardiac hypertrophy was noted on examination. A harsh, grade 4 systolic murmur was heard over the precordium with its maximum intensity in the second and third left interspaces in the parasternal line. No definite diastolic component was heard. Some clubbing and cyanosis of the nails was noted. Roentgenograms revealed questionable evidence of hypertrophy of the right ventricle. No pulmonary window was demonstrated. Electrocardiograms revealed right axis deviation. The hemoglobin content, as determined by the photoelectric cell method, was 18.5 Gm per hundred cubic centimeters of blood, and the erythrocyte count was 5,700,000 per cubic millimeters.

Venous catheterization of the heart revealed the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %	Blood Pressure
Superior vena cava	11.03	30.5	
Right atrium	11.51	31.7	12/0
Right ventricle	12.71	31.3	78/4
Right pulmonary artery	13.23	34.0	3/2
Femoral artery	24.20	17.2	

An increase in oxygen content in the right ventricle over that in the right atrium was somewhat suggestive of a left to right shunt, and definite evidence of a septal defect was obtained by passing a catheter into the pulmonary vein, with its greatly increased oxygen content. The combination of a large increase in pressure in the right ventricle and an extremely low pressure in the pulmonary artery was evidence of stenosis of the pulmonary infundibulum. The lowered oxygen saturation (72 per cent) in the femoral artery, in conjunction with the electrocardiographic and roentgenographic evidence, completed the diagnosis of tetralogy of Fallot.

A Blalock operation with anastomosis of the left subclavian artery and the left pulmonary artery was performed, with good results.

Associated with Patent Ductus Arteriosus. A case of cyanosis was recorded in which the catheterization findings were similar except that there was an increase of the oxygen content from the right ventricle (14.1 volumes per cent).

to the right pulmonary artery (187 volumes per cent) We believe that this difference indicates an associated patent ductus arteriosus The oxygen saturation in the femoral artery was 81 per cent, no operation has been performed at the time of writing

It is not to be expected that the tetralogy of Fallot can be recognized in its entirety by study with the venous catheter alone Dextro-position of the aorta is largely a morphologic diagnosis, the condition is functionally indistinguishable from a ventricular septal defect in studies with the venous catheter Hypertrophy of the right ventricle is perhaps best indicated by the electrocardiograms The catheter may pass from the right ventricle through the stenotic pulmonary valve into the pulmonary artery or through the septal defect into the aorta In the former instance, pulmonary stenosis may be recognized by the presence of a higher systolic pressure in the right ventricle than in the pulmonary artery In the latter instance, pulmonary stenosis may be assumed to be present if the systolic pressures in the aorta and the right ventricle are identical (Dexter¹²) Thus, intracardiac catheterization may be used in studying patients with congenital cyanotic heart disease to ascertain the presence or absence of associated left to right shunts (especially patent ductus arteriosus) which may be increasing pulmonary blood flow Too, the procedure may make available information about the pulmonary valve and artery and about the amount of flow through these structures

Recent studies by Blalock and Taussig^{1b} which led to the surgical treatment of congenital heart disease and cyanosis indicated the physiologic importance of a diminished rate of pulmonary blood flow in the production of anoxemia As observed by Bing and others,¹³ it is important to study quantitatively the changes in pulmonary blood flow in such conditions in order to correlate the primary abnormal factor with the accompanying hemodynamic and respiratory alterations The practical significance of preoperative recognition of pulmonary stenosis and atresia makes it advisable to study the results of physiologic tests

The essential factor in any operation on a patient with congenital cyanotic heart disease is to direct systemic arterial blood into the pulmonary artery so that an adequate proportion of the blood stream is oxygenated The operation should be undertaken only when pulmonic circulation is inadequate and when systemic and pulmonary arteries can be used for or adapted to, the anastomosis By the method of venous catheterization and by exercise and respiratory tests, Bing and his associates¹⁴ studied many cases of tetralogy of Fallot and found that

13 Bing, R J , Vandorn, L D , and Gray, F D , Jr Physiological Studies in Congenital Heart Disease I Procedures, Bull Johns Hopkins Hosp 80 107, 1947

14 Bing, R J , Vandorn, L D , and Gray, F D , Jr Physiological Studies in Congenital Heart Disease II Results of Pre-Operative Studies in Patients with Tetralogy of Fallot, Bull Johns Hopkins Hosp 80 121, 1947

a collateral circulation frequently develops which is not revealed by application of the direct principle (Fick¹⁵), using the venous catheter. By utilizing certain formulas, Bing and his co-workers were able to evaluate, to a certain degree of accuracy, pulmonary artery flow, systemic blood flow, pulmonary capillary flow and collateral circulation to the lungs, among other processes. In 48 cases of tetralogy of Fallot, the results of these tests demonstrated a reduction in pulmonary artery of 1,000 to 2,000 cc below the normal cardiac index, depending on the degree of stenosis. In most of the cases, the systemic flow exceeded that through the pulmonary artery, indicating that the over-all direction of the intracardiac shunt was from right to left. The value of a combined determination of pulmonary artery flow and pulmonary capillary flow was demonstrated in 4 cases in the series in which clinical evidence suggested a patent ductus in addition to pulmonary stenosis. In cases of this type, the volume of flow through the ductus is represented by the difference between the pulmonary capillary flow and that in the pulmonary artery. An estimate of the rate of blood through the patent ductus is of considerable importance, as surgical construction of an additional ductus by the Blalock-Taussig operation may be indicated if the natural anastomosis is too small.

Common Atrium with Possible Tricuspid Atresia B. T., a woman of 18, had been born a blue baby and had continued to be moderately cyanotic. Progressive clubbing of the fingers and toes had been noted by the patient. She was able to walk three to four blocks without undue shortness of breath and occasionally danced. For the past few months, there had been slight intermittent swelling of the ankles.

Physical examination showed a cyanotic, slender, somewhat underweight white woman with pronounced clubbing of the nails. The left border of the heart was at the anterior axillary line. There were no murmurs present. There was a sinus rhythm, the rate being 102 beats per minute. The blood pressure was 98 systolic and 74 diastolic. The rest of the physical examination was essentially noncontributory.

Electrocardiograms, including all precordial leads, revealed hypertrophy of the left ventricle. Stethograms failed to show any murmurs. Roentgenograms of the chest revealed suggestive evidence of hypertrophy of the left ventricle. The pulmonary artery could not be identified.

Venous catheterization studies yielded the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %	Blood Pressure
Superior vena cava	10.79	40.0	
Right atrium or common atrium	12.72	35.0	15/10
Right atrium or common atrium	10.31	40.0	
Site of vigorous pulsation, appar- ently just inside right ventricle	12.50	35.0	?
Pulmonary vein	29.97	23.8	8.10/3.4
Femoral artery	24.46 (saturation, 68%)		

15 Fick, A. Ueber die Messung des Blutquantums in den Herzventrikeln, Verhandl. d. phys. med. Gesellsch. zu Würzburg 2:16, 1870.

The catheter could be seen coiled in the large atrial chamber. Various oxygen values were observed, an increase of 1.92 volumes per cent of oxygen in the atrium over that in the superior vena cava was noted, suggesting an atrial defect with a left to right shunt. The catheter was passed into a pulmonary vein entering the right border of the heart. Multiple attempts were made to insert the catheter into the right ventricle, on one occasion, a most vigorous pulsation was noted in the tip of the catheter as it was thought barely to have entered the right ventricle, but pressure values could not be obtained. However, samples indicated that the values for oxygen content were similar to the higher values in the atrium. The tip of the catheter buckled each time an attempt was made to push the catheter farther into the ventricle.

We considered the possibility of a large defect in the atrial septum accounting for an intermingling of the blood and the possible production of cyanosis. Oxygen saturation in the femoral artery was reduced to 68 per cent. A pulmonary vein was found to be emptying into what appeared to be the common atrium. Because of the difficulty in passing the catheter into the right ventricle and because of the electrocardiographic and roentgenographic evidence of hypertrophy of the left ventricle, a diagnosis of possible tricuspid stenosis or atresia was also entertained in addition to that of the atrial septal defect. A similar case was recently reported by Geraci and his associates¹⁶.

Special Conditions—Dilated Pulmonary Artery with Hypoplastic Aorta. R. R., a white man of 43, was admitted to the hospital complaining of having had shortness of breath for about three months. The present illness had begun approximately one and one-half years before, when he had been admitted to another hospital because of an abnormal roentgenogram of the chest, the condition was diagnosed as "heart disease," according to the patient. In June 1947, a chest cold developed. The patient was hospitalized, but the condition cleared and he was discharged. After this, he first noticed dyspnea on exertion, substernal pain that occasionally radiated to both shoulders and arms and several episodes of nocturnal dyspnea.

Physical examination showed a small, fairly well developed white man in no distress. The blood pressure was 135 systolic and 80 diastolic. The chest showed some slight prominence of the left side of the precordium. The heart was not enlarged to the left on percussion, and no thrills were felt. A short, grade 1 systolic murmur was heard over the second left interspace but was not always constant and showed no transmission.

The electrocardiogram was slightly abnormal, showing a deep S_I, a diphasic T_{II} and an inverted T_{III} wave. The P_{II} wave was pointed and prominent. Fluoroscopy showed a greatly dilated and pulsating pulmonary conus with dilated left and right pulmonary branches. The aortic knob was somewhat hypoplastic (fig 6). Catheterization studies showed the oxygen content to be equal in all the chambers. The patient required no specific treatment other than rest.

Because of the clinical and roentgenographic findings and the results of catheterization a diagnosis of "*grosse pulmonaire—petite aorte*," as made by

16 Geraci, J. E., Dry, T. J., and Burchell, H. B. Atrial Septal Defect and Probable Tricuspid Atresia in Adults, Proc. Staff Meet., Mayo Clin. **23**: 510, 1948.

Laubry and his associates¹⁷ in 1941, was entertained. They presented data concerning 39 patients personally seen by them who had shown the same syndrome as that of interatrial septal defect. Their failure to find a defect in 7 of the 8 cases at necropsy led them to conclude that malposition of the septum in the fetal truncus arteriosus was the etiologic factor. The final diagnosis in each case was dilated pulmonary artery and hypoplastic aorta.

Pulmonary Arteriovenous Aneurysm A M, a woman of 20, gave a history of having had a mild degree of cyanosis since birth. Starting one year before the patient's admission to the hospital, sporadic, transient, unconscious "spells" had begun to develop, at times, they were convulsive in type. Their frequency increased considerably during the year before admission, and two of the spells were accompanied with hemoptysis. The patient's gums bled rather easily for a few weeks before admission. There was mild limitation of her physical activity.

Physical examination revealed a listless, moderately cyanotic woman with pronounced clubbing of the finger nails and toe nails. A small hemorrhagic lesion was noted on the lower lip. Several prominent veins were noted in the mucous

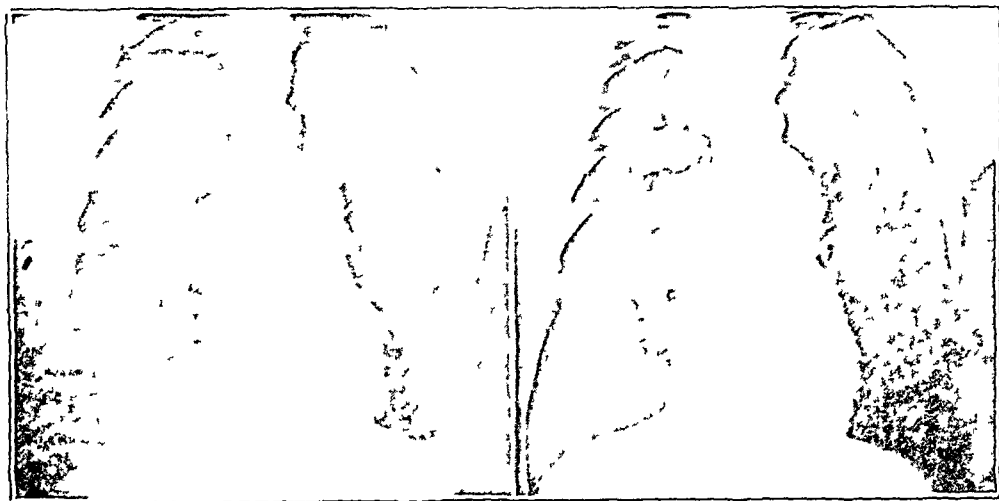


Fig 6—Teleroentgenograms revealing a dilated pulmonary artery and a hypoplastic aorta ("*grosse pulmonaire, petite aorte*")

membrane lining the mouth. Marked venous engorgement was noted on fundoscopic examination. The heart was not enlarged, the rhythm was regular and no murmurs were heard. The rate was 86 beats per minute. There was a rapid, 40 point drop in the systolic and diastolic arterial pressures on standing, the previously normal blood pressure had been 118 systolic and 72 diastolic. Gross examination of the lung failed to reveal any abnormalities, and no murmurs were heard.

A teleroentgenogram revealed a normal-sized heart with a lesion in the lower field of the right lung, in which there was a suggestion of a few cryptic cavities (fig 7). Pulmonary markings were increased in both lung fields. Electrocardiograms revealed a vertical heart but were otherwise unremarkable. The hemoglobin value, as determined with the photoelectric cell, was 22.0 Gm. The erythrocyte count was 7,400,000.

¹⁷ Laubry, C., Routier, D., and Heim De Balsac, R., *Grosse pulmonaire, Petite aorte, Affection congénitale*, Bull et Mém Soc méd d hôp de Paris 56 847, 1941.

Venous catheterization studies revealed the following data

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	13.2	
Right atrium	13.6	5/3
Right ventricle	13.5	20/0
Right pulmonary artery	13.5	3/0
Left pulmonary artery	13.4	3/0

It was thought that this patient had a pulmonary arteriovenous fistula, despite the absence of a continuous murmur over the lung shadow or at any place in the

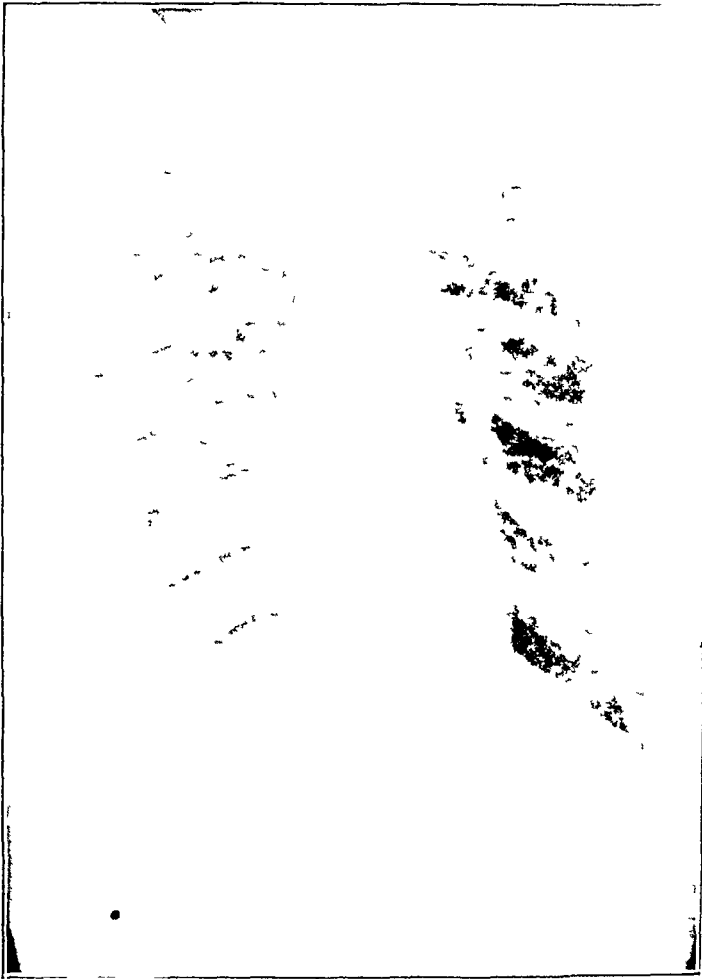


Fig 7—Teleroentgenogram revealing a normal-sized heart and an infiltrative area in the base of the right lung. The patient had a pulmonary arteriovenous aneurysm.

hilar regions. The history of convulsions, hemoptysis and cyanosis coupled with polycythemia and a shadow of the parenchyma of the lung suggested the clinical diagnosis. Catheterization studies were within normal limits. An attempt at the administration of iodopyracet injection (diodrast®) with the catheter in the right pulmonary artery had been planned, but the patient stated that she felt a convulsion coming on at the end of the catheterization, and further manipulation was abandoned. The convulsion, however, failed to materialize. (It is thought that catheterization studies would be of definite benefit in such cases to localize the site of an arteriovenous anastomosis.) Within the next few days, the patient

went into a profound coma and died before surgical intervention was attempted. Postmortem studies revealed a large pulmonary arteriovenous aneurysm.

Normal Hearts—The next group of patients studied was composed of children with heart murmurs that were thought by some examiners to be indicative of congenital heart disease. However, normal values for pressures and gas volumes were obtained. Venous catheterization studies may be of definite value in ruling out a diagnosis of suspected congenital heart disease and may greatly allay the fear of parents.

Diagnosis Impossible Because of Insufficient Data—In the remaining 3 cases, insufficient data were obtained to make a diagnosis. In 2 of these, in which patent ductus arteriosus was suspected, we were unsuccessful in getting the catheter into the pulmonary artery. In the third case, we were unable to get the catheter into the right ventricle.

Complications—We have had no major complications. Occasionally ventricular premature beats appear, especially when the catheter is close to the atrioventricular valve, but they do not persist. Atrial fibrillation¹⁸ has been reported, but this was controlled, and it disappeared when the catheter was removed. Superficial phlebitis of the antecubital veins developed in 3 cases but responded readily to local therapy. In 1 case, while using a smaller-sized catheter, we encountered plugging of the catheter and were forced to discontinue the procedure. On a few occasions, we have found it necessary to change catheters. In 2 cases, in children, the smallness of the veins prevented introduction of the catheter. In 1 case, there was retention of the catheter and it had to be removed with the patient under anesthesia, in another case, we were unable to get the catheter past the first rib, perhaps because of an associated abnormality of the venous system.

SUMMARY AND CONCLUSION

Intravenous catheterization of the heart in 72 cases of suspected congenital heart disease is discussed. The method and the application of it to the more accurate diagnosis and the study of the disturbed physiology of congenital heart disease are presented with a notation of the complications that may be encountered. The results of this method in 69 cases are given, and several detailed case reports representative of the acyanotic, potentially cyanotic and cyanotic types of heart disease as well as of pulmonary arteriovenous aneurysm and dilated pulmonary artery with hypoplastic aorta are given.

Venous catheterization has opened new possibilities for the recognition of many congenital defects, for elucidating the hemodynamic changes and for assisting in rendering a prognosis by defining the nature and the physiologic magnitude of the defects. Precise diagnosis is of such importance that all patients whose condition is doubtful should be studied with available diagnostic technics.

This work was aided by Dr L. Vaughn, roentgenologist, and Miss Anne Bray and Miss Peggy Gallagher, technicians.

18 Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibe, R. E., and Evans, J. M. Studies of Congenital Heart Disease. I. Technique of Venous Catheterization as a Diagnostic Procedure, *J. Clin. Investigation* 26:547, 1947.

Book Reviews

Coronary Artery Disease By Ernst P. Boas, M.D., and Norman F. Boas, M.D.
Price, \$6 Pp 399, with 88 illustrations Chicago Year Book Publishers, 1949

The Drs. Boas have written a commendable monograph on "Coronary Artery Disease." The arrangement is practical and logical, and the diction is clear. The authors' claim that the book is designed as a useful tool for the physician and that it is also sufficiently detailed to make it of interest to the cardiologist is valid. The extensive bibliography is well selected, and, in the reviewer's opinion, the appearance of supporting references as footnotes on the appropriate pages has distinct advantages.

The anatomic, embryologic, physiologic and pathologic aspects of the coronary circulation are covered in the earlier chapters. The approach to the subject is that of the clinician who has had wide first hand experience with diseases affecting the coronary circulation and, through it, the myocardium. Emphasis is placed on the restorative and compensatory mechanism inherent in the coronary circulation.

The opinions expressed on the diagnostic aspects of coronary heart disease are concise, yet, at the same time, they cover the variables in the pathologic aspects of coronary heart disease and the corresponding variables in the clinical picture. This is true of the acute episodes of the disease as well as of the more chronic phases of coronary insufficiency. The differentiation of the pain of angina pectoris from that due to noncardiac conditions producing pain in the thoracic structures is unusually well handled. The importance of recognizing what the authors refer to as "benign precordial pain," so frequently encountered in anxiety states either in association with, or often independent of, organic heart disease is well illustrated by a quotation (page 167): "The patient with true anginal pain reports very simply and without dramatic embroidery that walking, strain or excitement induces some form of sensation in the chest, or at times in the arm alone, which compels an arrest of activities. After a few minutes' quiet the distress is gone and the patient feels as well as ever. In contrast to this simple, clear story, the account by the individual with benign precordial pain is a highly colored version of sharp chest pains with all kinds of associated symptoms and vasomotor disturbances. He is not compelled to immobility, but lies down and rests and is overcome with bodily weakness, largely from apprehension."

The role of the electrocardiogram in the recognition, management and prognosis of coronary heart disease is supported by well selected illustrations. In the majority of instances, the authors use the precordial leads CR₂, CR₄ and CR₆ in conjunction with the standard limb leads. In discussing the outlook in coronary heart disease, the authors give a true perspective of the life history of coronary heart disease and point out the invalidity of most of the statistical data reflecting prognostic trends, as reported in much of the medical literature.

The authors are outspoken in their views on the actions of many drugs which have been and still are in use in the treatment of coronary heart disease. This material should be of assistance to interns and less experienced men of the profession who may be confused by the controversial statements and divergent claims made by many authors throughout the extensive literature on these subjects.

Sections dealing with treatment cover every phase of the disease. Here, again, the statements are clear and to the point. In any treatise covering a subject such as coronary heart disease it would be impossible to present opinions that would be unanimously accepted by all authorities. There is certainly no fault to

be found with the major issues presented, although there may be some difference of opinion about some of the minor ones

In the reviewer's opinion, this book is one of the best contributions to the field of cardiology in recent years

Symposium on Diseases of the Skin The Medical Clinics of North America Chicago number, January 1949 Pp 292, with 134 illustrations Philadelphia W B Saunders Company, 1949

This volume comprises a symposium on diseases of the skin, the contributors, with the exception of Drs O'Leary, Curtis, Grekin and Duncan, being dermatologists residing in Chicago

Subject matter was evidently chosen because of special interest in certain fields on the part of the various well known contributors In general, each author discusses his problem from the standpoint of clinical manifestations, laboratory findings, etiology, differential diagnosis and treatment Actual case reports and illustrations are included in many of the papers

Dr Becker presents a clear and logical interpretation of neurodermatitis and pruritus Dr O'Leary's discussion of dermatomyositis is especially interesting from the standpoint of differential diagnosis Drs Curtis and Grekin review the problem of sarcoidosis and include an informative paragraph on involvement of the eye Drs Rothman and Walker discuss the salient features of both diffuse and localized scleroderma Dr Senear gives a short but lucid interpretation of dermatitis exfoliativa, unburdened with descriptions from the older literature Dr Ebert's discussion of the herpes problem and Dr Rattner's discussion of pemphigus are well done Dr Rostenberg's presentation on cutaneous allergic disorders reflects his intense interest in and personal interpretation of allergy

Other problems discussed are skin cancer, under several titles, by Drs Oliver, Squire, Finnerud and Duncan, nail changes following the use of "base coats," by Dr Mitchell, disseminated lupus erythematosus, by Drs Graffin, Taylor and Hass, atopic dermatitis, by Dr Hetreed, common nevi, by Dr Webster, cutaneous pharmacodynamics of vehicles and drugs, by Dr Rothman and Dr Shapiro, and dermatopathology as a window to internal disease, by Dr Caro

The volume is comparatively small, in large type and consisting of 292 pages, including 134 well chosen illustrations It does not attempt to review all diseases of the skin, but the articles are interesting, currently authoritative and easy to read This symposium should find interested readers in the fields of general practice and internal medicine as well as dermatology

Clinical Auscultation of the Heart By S A Levine, M D, and W P Harvey, M D Price, \$6 50 Pp 327, with 286 illustrations Philadelphia W B Saunders Company, 1949

A hundred and three years ago, Dr Henry I Bowditch of the Harvard Medical School wrote "The Young Stethoscopist," in which he described all that he could of auscultation of the heart, indeed, his colleague, Dr Henry J Bigelow, reviewing the book in *The Boston Medical and Surgical Journal*, complimented Dr Bowditch highly by saying that he had booked Laennec up to date and had compressed his genius into a prodigiously small volume

Now, two other authors from the Harvard Medical School continue "to book Laennec up to date" They have written an ingenious sequel to "The Young Stethoscopist," in which they discuss auscultation of the heart, not by means of the ear alone but by combining what the ear can hear with what the electrocardiograph reveals in regard to cardiac action and with what the eye sees of the heart sounds as they are photographed electrically

The result is a book of practical value and of great interest. The authors answer many of the riddles which Dr Bowditch found so perplexing among others, the causes of change in character of the heart sounds, the cause of a third or fourth heart sound, the significance of various cardiac irregularities and the clinical importance of the "*bruit de souffle*," the "*bruit de r pe*" and the "*bruit de scie*"—terms invented by Laennec in the days when the well brought up post-graduate student went to Paris to learn the art of physical examination.

Interspaced among many excellent illustrations is a great deal of clinical wisdom. Dr Bowditch advises his readers "Do not trouble yourself so much about nice distinctions of sound, but observe accurately, first, where the sounds are heard, second, where the focus of them is, and third, their combination with other physical and rational signs." Drs Levine and Harvey elaborate on the text in a happy vein.

Without further description of the new book, it is cheerfully advocated, in the words of the first Boston reviewer of "The Young Stethoscopist," as a book to be recommended with the conviction that whoever studies its precepts will be a wiser practitioner than he was before.

Medical Etymology By O. H. Perry Pepper, M.D. Price, \$5.50 Pp. 263
Philadelphia: W. B. Saunders Company, 1949.

Dr Pepper has done a great service to physicians and to medical students in compiling this extremely useful book on the etymology of medical terms. As the author says in the preface, it is not intended to be a dictionary, no roots are analyzed, declensions are not discussed, there are no elaborate discussions of gender. On the contrary, Dr Pepper sticks strictly to business and for the most part simply gives the meaning of the Latin or Greek word from which a medical term is derived. This is done with true Johnsonian terseness, barring an occasional comment or brief discussion which, indeed, is also worthy of the Great Lexicographer. Of course, the sad part of all this is that the very need of such a vademecum shows the depths to which modern education has fallen. A hundred years ago any second form boy (as Macaulay would have said) deserved and doubtless got a flogging for not knowing such elementary stuff. Dr Pepper agrees with this opinion but accepts the theory that "classical education is a dead letter for those entering the medical sciences and 'nothing can be done about it'." With this, the reviewer does not altogether agree. Wise men in all branches of education, including science, are realizing the need of reviving the means of firsthand acquaintance with the civilization from which our own is derived as well as realizing the value of the tremendous mental discipline which is to be gained from accurate translation of a foreign language. It has been said that the British won their battles on the playing fields of Eton, perhaps it was really in the classroom, struggling with Greek hexameter, that clear thinking and grit were acquired.

Be that as it may, "Medical Etymology" should certainly be on the required book list of every medical school at the present time.

Symposium on Cardiovascular Diseases, Especially Hypertension Medical Clinics of North America (New York number), May 1949 Pp. 911, with 190 illustrations Philadelphia: W. B. Saunders Company, 1949.

A symposium of cardiovascular diseases with emphasis on hypertension is featured in the New York number of the *Medical Clinics of North America*. The discussion opens with an encouraging article on the benign phase of hypertension, pointing out that it can exist for many years despite unfavorable roentgenographic

and electrocardiographic changes—a fact to be considered when evaluating either medical or surgical therapeutic results. There follows a group of articles on fundic alterations, electrocardiographic changes and capillary fragility as studied in hypertensive persons. Differential points between the electrocardiogram in hypertension and that in myocardial infarction are well demonstrated, as is the concept that metabolic and arteriosclerotic changes, and not hypertension per se, cause capillary fragility.

Therapy of the hypertensive patient is discussed in a series of articles covering both surgical and medical phases. The conservative regimen of sensible living habits, sedation and judicious administration of thiocyanate is offered as producing results comparable to the more radical procedures. On the other hand, the advocates of sympathectomy present statistics which warrant further consideration of this unsettled and controversial problem.

The remainder of the discussion of cardiovascular problems presents speculative and proved points in arteriosclerosis—the etiologic role of hormones and cholesterol, therapy and the relation of the disease to diabetes. In addition there are miscellaneous papers on psoriatic arthritis, on relapsing pancreatitis and on fluid and mineral balance in infantile diarrhea, all of which are adeptly written and serve to round out an excellent number of the *Medical Clinics of North America*.

Archives of Internal Medicine: The Epidemiology of Hemolytic Streptococcus. By Alvin F. Coburn and Donald C. Young. Price, \$4. Pp 229, with 31 illustrations and 51 tables. Baltimore: The Williams & Wilkins Company, 1949.

The authors of this book deserve high praise for the interesting way in which they have assembled a vast mass of material. As they state in the preface, the thought of making nationwide observations on streptococcal activity seemed of only academic interest until lately, the war, however, made the need of practical and essential significance.

Dr. Coburn and Dr. Young were in a position to follow a wise bit of Oslerian advice—"Observe, tabulate and record." In this monograph, therefore, they record the results of observing and tabulating the effect of the streptococcus on young men in training for Naval service.

They were helped in all possible ways by epidemiologists, bacteriologists, clinicians and statisticians, as well as by patients themselves. The result is a valuable account of composite medical experience. It is interesting for a practicing doctor to read, for it describes so clearly how streptococcus infections are likely to spread through any community, it is an important work for physicians interested in public health, because so much valuable material is reported, it is a fine piece of medical literature for students because it is written clearly and concisely, and because it reveals how clinical research in the field of infectious disease can be conducted, what methods are available and how conclusions are drawn by the judicious and unprejudiced analysis of carefully accumulated data. On the whole, it is a contribution to medicine in which the Bureau of Medicine and Surgery of the United States Navy may well take pride.

Diagnosis of Viral and Rickettsial Infections. By Frank L. Horsfall Jr., M.D. Price, \$3.75. Pp 153, with 4 illustrations, 7 plates and 14 tables. New York: Columbia University Press, 1949.

On Jan. 29 and 30, 1948, a symposium on the diagnosis of viral and rickettsial infections was held in the New York Academy of Medicine. After brief introductory remarks by Dr. Horsfall, of the Hospital of the Rockefeller Institute, twelve papers were presented. These dealt with laboratory procedures usable in

studying viruses and with the diagnosis of mumps, the psittacosis-lymphogranuloma group of infections, primary atypical pneumonia, neuropathic virus infections, herpes simplex, rabies, dengue, infectious mononucleosis, Rocky Mountain spotted fever and infectious hepatitis. Each of the papers was presented briefly and pointedly by an authority on the topic under consideration. The volume in which the papers are compiled is informative and of unusual interest.

Those who enjoy attempting to trace the development of medical knowledge may recall that a similar symposium was held nearly a decade ago at the Harvard School of Public Health, although chief emphasis was laid on the significance of virus and rickettsial diseases in public health, laboratory procedures and diagnoses were included. Thus, the book, "Virus and Rickettsial Diseases," printed in 1940 and reporting the Harvard symposium, is interesting to study beside "Diagnosis of Viral and Rickettsial Diseases," printed nine years later. Either book alone deserves a place in any medical library, the two beside one another make a handsome pair. In comparing them, one feels that Hans Zinsser and other virologists who were active only a few years ago must be proud of the record.

George R Minot Symposium of Hematology Edited by William Dameshek, M.D., and F. H. L. Taylor, Ph.D. Price, \$12. Pp 984. New York: Grune & Stratton, 1949.

This is a notable volume, dedicated by a group of his friends to Dr. George R. Minot, who, besides being a Nobel prize winner, is a sociable person—the kind of man well liked by his pupils, associates and professional colleagues.

The book deals mainly with diseases of the blood, properly enough, it begins with a reprint of that historic paper written by Minot and Murphy in 1926, "Treatment of Pernicious Anemia by a Special Diet." Then follow articles on pernicious anemia, hemolytic anemia, other anemias, hemorrhagic diseases, leukemia, the cytology and biochemistry of the red and white cells and, finally, two papers on more general aspects of medicine, one from Gunnar Alsted of Copenhagen on peptic ulcer, and one from W. Richard Ohler of Boston on diabetic coma.

There are eighty-four articles in the entire collection, each is written by an authoritative worker in his field, and they are printed tastefully in a well designed and well illustrated volume. Every writer seems to have been stimulated to prepare his manuscript in a fashion sufficiently meticulous to satisfy Dr. Minot's respect for detail, accuracy and imagination. Thus, the result not only is a pleasing symbol of friendship for one of the leading internists and clinical investigators of his day but also is a valuable reference source for any one wishing to learn of the most recent advances in hematology.

Oral and Dental Diagnosis By K. H. Thoma, D.M.D. Third edition. Pp 563, with 776 illustrations. Philadelphia: W. B. Saunders Company, 1949.

The first edition of this book, 379 pages long and including 533 illustrations, appeared in 1936. A second edition, a little bigger and better than the first, was necessary in 1943. Now the third edition has appeared, the book has grown in stature to comprise 563 pages and 776 illustrations.

The basic model of the volume remains unchanged. It describes how important it is for physicians to examine the oral cavity properly, always bearing in mind that a variety of systemic disorders may make an early appearance in the mouth. It also describes, in great detail, oral diseases in general and their diagnosis and treatment in particular.

Both earlier editions were reviewed favorably in *The Journal of the American Medical Association* (108 1209 [April 3] 1937, 124 469 [Feb 12] 1944) THE ARCHIVES is glad to welcome the third edition and to emphasize what was stated in previous reviews, that the book is a textbook to be used by students and physicians as well as by dentists and oral surgeons. For if the field of dental medicine is to be opened widely, it must be explored adequately—not by specialists working in a narrow area but, broadly and extensively, by groups of physicians working together. From this point of view, the book is an important source of reference.

Manual of Medical Emergencies By S C Cullen, M D, and E G Gross.
M D Price, \$3.75 Pp 267, with 29 illustrations Chicago Year Book Publishers, Inc, 1949

The authors of this book are professors in the State University of Iowa College of Medicine and apparently enjoy teaching. They have assembled an admirable manual. As the title foretells, it deals with the treatment of the kind of emergencies which any doctor is likely to encounter—emergencies that require artificial respiration or the use of oxygen, circulatory emergencies, poisonings, burns, comas and serious anaphylactic reactions.

The book is written positively, it gives intelligent, readily understandable advice in regard to the management of a variety of accidents, and the fact that it is so dogmatic makes it all the more readable.

The illustrations are also helpful, a few cartoons that have been introduced are not particularly cogent.

The book is of a size and shape to fit easily into one's bag or pocket. On the whole it should be of great service, as its dedication suggests, to the general practitioner, who is expected to see all, know all and do all in the field of medicine.

Studies of Chronic Pyelonephritis By Flemming Raaschou, M D Pp 260, with 61 illustrations Copenhagen Einar Munksgaard, 1948

This monograph was prepared as a doctor's thesis at the University of Copenhagen. It has been translated into English and gives a thorough and detailed account of chronic pyelonephritis.

The discussion of the history of the disease and its pathology is well written. The analyses of the age and sex distribution of pyelonephritis and of its frequency and its clinical course are adequate. Chief emphasis is placed on the author's studies on renal function, in which he describes his observations of glomerular and tubular function in a series of cases. He has used urea clearance and inulin and iodopyracet injection (diodrast®) in a variety of ways, attempting to prove what modern tests for renal function can demonstrate in the study of the pyelonephritic kidney. He gives a good summary of the literature.

On the whole, this is a painstakingly written volume. It should prove useful as a source of reference for those who, like the author, are interested in renal physiology and for those who wish to learn how transatlantic colleagues are attacking its complex problems.

Anales de la cátedra de clínica médica (Volume II), 1947 By E S Mazzei, M D Annual publication of the University Clinic Pp 267 Buenos Aires "El Ateneo," 1948

The book is a collection of selected material for lectures to medical students. Little original material is presented, with the exception of a short and interesting article by de la Torre on the treatment of acute glomerular nephritis by the

intravenous injection of procaine hydrochloride (novocaine®) Three cases of acute glomerular nephritis following scarlet fever are described in which this treatment was given with spectacular results The rest of the articles are mostly complete and excellent reviews of recent advances of American and French medicine An article by Bergna on Hr factor is particularly exhaustive American readers will find of special interest a well organized monograph by Reussi on bronchopulmonary topography and its applications to the studies of the pathology and treatment of pulmonary disorders The format of the book is excellent, the bibliographic references are complete and well arranged

An Atlas of Electrocardiography By W Dressler, M D, and H Roesler, M D Price, \$14 Pp 503, with 439 illustrations Springfield, Ill Charles C Thomas, Publisher, 1949

This atlas is not particularly different from others available It consists of photographs of electrocardiograms presented on one page with clinical and other related data and the electrocardiographic data on the opposite page This conventional procedure of making the tracing and the discussion available to the reader simultaneously is obviously a good one Some interpretations are documented with postmortem findings Unfortunately, the chest leads presented in most of the cases consist of CF and CR leads rather than unipolar leads If these leads are to be presented the unipolar leads should not be excluded As the authors state, the atlas is not intended for beginners, it may be of value to others

Present Concepts of Rehabilitation in Tuberculosis By Norvin C Kiefer, M D Price, \$3 50 Pp 398 New York National Tuberculosis Association, 1949

This excellent book comprises a review and analysis of some 1,000 papers on the subject of rehabilitation in tuberculosis Being really a series of abstracts it lends itself poorly to review, the main value is as a reference book Here, in classified form, one finds material on such matters as agencies, types of program, and personnel The book will be invaluable to public health officers and to all persons interested in tuberculosis

Female Sex Endocrinology By Charles H Birnberg Price, \$4 Pp 134, with 30 illustrations Philadelphia J B Lippincott Company, 1949

This is a readable and concise handbook of female endocrinology It is written so simply that lay women as well as medical students and practicing physicians of both sexes can learn from it It gives an up-to-date account of its subject and explains some of the new terms and remedies that are achieving popularity While not a great book, it promises to fill a useful purpose

Food Poisoning By G M Dack, M D Revised edition Price, \$3 75 Pp 184 with 13 tables Chicago University of Chicago Press, 1949

This is a brief monograph on food poisoning, written, with able assistance, by an authority on the subject The data are presented in more or less the usual textbook of medicine fashion It is to be recommended highly for clinicians, students and bacteriologists

ROLE OF BLOOD PLATELETS IN THROMBOEMBOLISM

SYLVAN E MOOLTEN, M D

LEO VROMAN

GEORGINE M S VROMAN

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NEW BRUNSWICK, N J

DEVELOPMENT OF MODERN CONCEPTS OF THROMBUS FORMATION

IN THE first half of the nineteenth century, thrombosis of blood vessels was held to result either from excessive coagulability of the blood or from exudative inflammation of the vascular wall. Virchow's views¹ influenced subsequent thought on the subject of intravascular clotting by their stress on the importance of slowing or stagnation of blood flow as well as on altered "molecular attraction" between the blood and the vascular wall.

By means of experiments in living animals, Mantegazza² (1869, 1871) and Zahn³ (1875) assembled proof that thrombosis is not equivalent to simple clot formation but consists primarily in a process of selective precipitation of protoplasmic elements from the flowing blood at sites of vascular injury to form a homogeneous, grayish white deposit (the "white thrombus"). With complete occlusion of the lumen by the white thrombus, the blood which is trapped in a column quickly clots to form a cast of the vessel (the "red thrombus"). The same principle (formation of an occlusive white thrombus followed by clotting of whole blood) was shown to hold also for the closure of puncture defects in veins (Zahn³).

From the Research Division, Laboratory Service, St. Peter's General Hospital.

This study was aided by grants from the Dazian Foundation, Dr. F. M. Clarke and Mr. Harry Hillman.

1 Virchow, R. *Gesammelte Abhandlungen zur wissenschaftlichen Medizin*. Frankfurt a. M., Meidinger Sohn u. Comp., 1856, cited by Eberth, J. C., and Schimmelbusch, C. *Experimentelle Untersuchungen über Thrombose*, Virchow's Arch f. path. Anat. **103**:39, 1886, **105**:331 and 456, 1886.

2 Mantegazza, cited by Bizzozero, J. *Ueber einen neuen Formbestandtheil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung*, Virchow's Arch f. path. Anat. **90**:261, 1882.

3 Zahn, F. W. *Untersuchungen über Thrombose. Bildung der Thromben*, Virchow's Arch f. path. Anat. **62**:81, 1875.

Through Bizzozero's epochal investigations ⁴ (1882), the mammalian blood platelets were properly classified and their key position in thrombosis was firmly established. Employing a technic of direct observation of the vessels in the guinea pig omentum he repeated experiments of Jones ⁵ (1850), Mantegazza ² and Zahn ³ and proved that the white thrombi which form at sites of mechanical or chemical injury are composed principally of agglutinated platelets which gradually become fused into a granular viscous substance. Clotting occurs in the wake of the changes in the platelets. Agents which prevent or retard blood clotting were found to inhibit platelet alteration. Bizzozero noted further that fibrin is deposited in a blood vessel only when platelets have previously become attached to its lining.

Osler, ⁶ who had also studied the clumping of platelets, reported them to be the chief component of vegetations on cardiac valves and of mural thrombi of the aorta or of aortic aneurysms. Hayem, ⁷ at about the same time, established the importance of platelets in the arrest of hemorrhage. They were shown to form an effective hemostatic plug by their agglutination to the edges of a vascular defect in advance of clotting.

Later workers ⁸ confirmed these data and extended knowledge in several directions. It has become a commonplace observation that agents which inhibit clotting also suppress or delay platelet adhesiveness, agglutination and lysis, ⁹ retard thrombus formation ¹⁰ and may impair

4 Bizzozero, J. Ueber einen neuen Formbestandtheil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung, *Virchows Arch f path Anat* **90** 261, 1882.

5 Jones, T. W. On the State of the Blood and the Blood-Vessels in Inflammation, Ascertained by Experiments, Injections, and Observations by the Microscope, *Guy's Hosp Rep* **7** 1, 1851.

6 Osler, W. Ueber den dritten Formbestandtheil des Blutes, *Centralbl f d med Wissensch* **20** 529, 1882, On Certain Problems in the Physiology of the Blood Corpuscles, *M News* **48** 365, 393 and 421, 1886.

7 Hayem, G. Sur le mecanisme de l'arrêt des hemorrhagies, *Compt rend Acad d sc* **95** 18, 1882.

8 (a) Schimmelbusch, C. Die Blutplättchen und die Blutgerinnung, *Virchows Arch f path Anat* **101** 201, 1885. (b) Eberth, J. C., and Schimmelbusch, C. Experimentelle Untersuchungen über Thrombose, *ibid* **103** 39, 1886, **105** 331 and 456, 1886. (c) Welch, W. H. Thrombosis, in Albutt, T. C. *A System of Medicine*, London, Macmillan & Co., 1899, vol 7, p 155, reprinted in *Papers and Addresses*, Baltimore, Johns Hopkins Press, 1920, vol 1, p 110. (d) Aschoff, L. Thrombosis, in *Lectures on Pathology*, New York, Paul B Hoeber, 1924, chap 11, Thrombose und Embolie, *Verhandl d deutsch Gesellsch f Kreislaufforsch* 1934, p 11.

9 (a) Bizzozero ⁴. (b) Burkner, K. Blutplättchen und Blutgerinnung, *Arch f d ges Physiol* **102** 36, 1904. (c) Aynaud, M. N. Le globulin des mammiferes, *Thesis*, Paris, no 93, 1909. (d) Deetjen, H. Zerfall und Leben der Blutplättchen,

hemostasis¹¹ As a corollary, it is also accepted by many authorities that thrombus formation as well as hemostasis depends not only on the availability of a sufficient number of platelets¹² but also on their capacity to adhere and to undergo lysis¹³

ROLE OF PLATELETS IN VASCULAR PHYSIOLOGY

The normal rate of formation and destruction of platelets has not been determined accurately After marked reduction in their number, one third of the entire normal amount can be regenerated in twenty-four

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10 (a) Aplitz, K Ueber den Bau junger Blutplättchenthromben und den Einfluss des Novirudins auf ihre Entstehung *Centralbl f allg Path u path Anat* **50** 9, 1930 (b) Best, C H, Cowan, C, and Maclean, D L Heparin and the Formation of White Thrombi, *J Physiol* **92** 20, 1938 (c) Zucker, M B Platelet Agglutination and Vasoconstriction as Factors in Spontaneous Hemostasis in Normal, Thrombocytopenic, Heparinized and Hypoprothrombinemic Rats, *Am J Physiol* **148** 275, 1947 (d) Dale, D U, and Jaques, L The Prevention of Experimental Thrombosis by Dicoumarin, *Canad M A J* **46** 546, 1942

11 (a) Jurgens^{9j} (b) Zucker^{10c} (c) Dale and Jaques^{10d} (d) Jurgens, R Beitrag zur Pathologie und Klinik der Blutungsbereitschaft, *Ztschr f klin Med* **123** 649, 1933

12 (a) Hayem⁷ (b) Welch^{8c} (c) Aschoff^{8d} (d) Quick^{9k} (e) Frank, E Hamorrhagische Diathesen, in Klemperer, G, and Klemperer, F Neue deutsche Klinik, Berlin, Urban & Schwarzenberg, 1930, vol 4, p 935

13 (a) Jurgens^{11d} (b) Baar, H, and Székely, L Über die Plättchenzerfallsgeschwindigkeit bei normalen Kindern, bei der Hamophilie und Thrombopenie, *Ztschr f Kinderh* **48** 31, 1929 (c) Baar, H The Stickiness of Platelets, *Lancet* **2** 775, 1941 (d) Wright, H P Changes in the Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, *J Path & Bact* **54** 461, 1942 (e) Silberberg, M The Causes and Mechanism of Thrombosis, *Physiol Rev* **18** 197, 1938 (f) Aggeler, P M, Howard, J, and Lucia, S P Platelet Counts and Platelet Function, *Blood* **1** 472, 1946 (g) Jurgens, R, and Naumann, W Klinische und experimentelle Untersuchungen über Funktionen der Blutplättchen, *Deutsches Arch f klin Med* **172** 248, 1931 (h) Tocantins, L M The Mechanism of Hemostasis, *Ann Surg* **125** 292, 1947 (i) Aplitz, K Die Dukessche Probe, *Ztschr f d ges exper Med* **111** 554, 1942

hours⁹⁵ According to Tocantins,¹⁴ the principal site of platelet destruction is the peripheral circulation Evidence exists that the platelets may be physiologically concerned in controlling capillary permeability to water and plasma proteins (Danielli¹⁵) Vasoconstrictor activity has also been shown to occur in the products of platelet lysis and has been credited with an important role in hemostasis¹⁶ In idiopathic thrombopenic purpura, the fragile, toneless, overfilled capillaries (Macfarlane¹⁷) and the wide differences in bleeding time in various parts of the body (Roskam^{9m}) may reflect not only a numerical lack of platelets but reduced platelet lysis (Reid,^{16c} Zucker^{10c}) and defective biologic activity as well As a corollary, there is the possibility that platelet lysis in the peripheral circulation plays a physiologic role in the normal contractility and tonus of the minute vessels (the pre-capillaries and venules) The labile character and activity of the platelets even more than their quantity may thus determine to an important degree the functional state of these vessels as measured by tests of bleeding time and capillary fragility As once stated by Howell and Donahue,¹⁸ the megakaryocyte "constitutes, so to speak, a unicellular gland which gives off a solid secretion in the form of platelets The eventual solution or disintegration of the platelets presumably adds to the plasma important constituents"

Recently, Zucker^{10c} imparted experimental evidence indicating that platelet vasoconstrictor substance is liberated rapidly from white thrombi and, by its diffusion locally, causes vasoconstriction within a considerable area According to Reid,¹⁹ this agent may be a factor, if not the sole factor, in maintaining vasoconstriction in the peripheral field

14 Tocantins, L M Arterial, Venous and Cutaneous Blood Platelet Counts in Men and Dogs Under Normal and Abnormal Conditions, *Am J M Sc* **192** 150 1936

15 Danielli, J F Capillary Permeability and Oedema in the Perfused Frog *J Physiol* **98** 109, 1940

16 (a) Zucker^{10c} (b) O'Connor (1912), Zucker and Stewart (1913), Janeway, Richardson and Park (1918), Freund (1920) and Reid and Bick (1942), cited by Zucker, M B A Study of the Substances in Blood Serum and Platelets Which Stimulate Smooth Muscle, *Am J Physiol* **142** 12, 1944 (c) Feissly, cited by Roskam^{9m} (d) Zucker, M B A Study of the Substances in Blood Serum and Platelets Which Stimulate Smooth Muscle, *Am J Physiol* **142** 12, 1944 (e) Reid, G A Preliminary Note on the Relationship of the Blood Platelets to the Mechanism of Hemostasis, *M J Australia* **2** 244, 1943

17 Macfarlane, R G Critical Review The Mechanism of Haemostasis *Quart J Med* **10** 1, 1941

18 Howell, W H, and Donahue, D D The Production of Blood Platelets in the Lungs, *J Exper Med* **65** 177, 1937

19 Reid, G Observations on the Part Played by the Vasoconstrictor Substance of Blood Platelets in the Mechanism of Vascular Spasm, *M J Australia* **2** 139, 1947

of an artery damaged, thrombosed or occluded by an embolus, provided the circulation is inadequate to remove it or it continues to be liberated. It is also conceivable that the platelet vasoconstrictor agent accounts for the arterial spasm which frequently complicates thrombophlebitis and which is commonly regarded²⁰ as a reflex originating in the inflamed venous wall.

PLATELET AGGLUTINATION AND ADHESIVENESS

The formation of blood platelets from ripened megakaryocytes of the bone marrow has been shown to depend on a process of partitioning occurring first in the cytoplasmic granules²¹ and later completed in the cytoplasm itself²². The individual platelets, formed in this manner, exhibit a remarkable tendency to remain dispersed in the normal circulation²³. Even after being crowded in the spleen, they may be liberated therefrom in large numbers after the injection of epinephrine (adrenalin®) and may remain separate from one another and free of any increased tendency to clump or adhere²⁴.

Under certain conditions, the platelets lose suspension stability²⁵ more readily even than erythrocytes or leukocytes^{8b} and clump rapidly with one another or on a favored surface. Factors in platelet agglutination are held to include (1) intrinsic changes in their protoplasm, probably lytic in character,²⁶ which render them more susceptible to the "spreading" action of a wettable surface²⁷ and (2) changes in the surrounding blood plasma which favor clumping of suspended particles. The plasmatic changes are said to include an increase in electronegative plasma proteins (globulins and fibrinogen), which partially cancels the negative charge on the surface of the platelets and so reduces the mutual repulsion which exists between them, as in the

20 Ochsner, A., and DeBakey, M. Thrombophlebitis. The Role of Vaso-spasm in the Production of the Clinical Manifestations, *J A M A* **114** 117 (Jan 13) 1940

21 Seeliger, cited by Frank, E. Die hamorrhagischen Diathesen, in Schittenhelm, A. Enzyklopadie der inneren Medizin, Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol 2, p 289

22 Dameshek, W., and Miller, E. B. The Megakaryocytes in Idiopathic Thrombocytopenic Purpura. A Form of Hypersplenism, *Blood* **1**.27, 1946

23 Osler⁶ Schimmelbusch^{8a} Eberth and Schimmelbusch^{8b}

24 Wright, H. P. The Sources of Blood Platelets and Their Adhesiveness in Experimental Thrombocytosis, *J Path & Bact* **56**.151, 1944

25 Osler⁶ Aynaud^{9c} Tocantins^{9g}

26 Bizzozzero⁴ Deetjen^{9d} Silberberg^{13e}

27 (a) Tait, J., and Elvidge, A. R. Effect upon Platelets and on Blood Coagulation of Injecting Foreign Particles into the Blood Stream, *J Physiol* **62** 129, 1926. (b) Tait, J., and Burke, H. E. Platelets and Blood Coagulation, *Quart J Exper Physiol* **16** 129, 1926, cited by Tait and Elvidge^{27a}

case of all particles carrying a like charge²⁸ A similar mechanism is implied in Roskam's idea that a pellicle of plasma protein, including fibrin, "opsonizes" the platelets and the surfaces to which they adhere²⁹

Since the time of Bizzozero, it has become generally recognized that conditions which cause platelets to adhere are essentially the same as those which initiate blood clotting, viz, contact with a "wetable" surface³⁰ or with injured tissue³¹ It has also become clear that such conditions can influence platelets much more readily than they can provoke clotting³² This is demonstrable, for example, in the fact that "white thrombi" appear before "red thrombi" in thrombotic disease of large vessels³³ Another example is found in the fact that a plug of agglutinated platelets (*clou hémostatique*) often seals the gap in an injured small vessel well in advance of clotting so that that process serves merely as secondary reinforcement against renewed bleeding³³ Additional evidence is the fact that in the living animal distinctly larger concentrations of heparin sodium or dicumarol[®] must be provided to inhibit formation of a white thrombus than to render the animal's blood incoagulable for many hours under experimental conditions which ordinarily result in thrombosis³⁴

Although it is not yet conclusively proved, it is likely that thrombin is the plasmatic factor primarily responsible for intrinsic alterations in blood platelets which result in their acquisition of "stickiness," in their agglutination and in their eventual complete dissolution³⁵ Amounts of

28 Starlinger, W, and Sametnik, S Ueber die Entstehungsbedingungen der spontanen Venenthrombose, *Klin Wchnsch* **6** 1269, 1927

29 Roskam, J (a) footnote 9*m*, (b) Le rôle du plasma dans l'agglutination des globulins (plaquettes), *Compt rend Soc de biol* **86** 733, 1922

30 (a) Bizzozero⁴ (b) Haydem⁷ (c) Footnote 9*d, e, f* and *k* (d) Tait and Elvidge^{27a} (e) Tait and Burke^{27b} (f) Lampert, H Die physikalische Seite des Blutgerinnungsproblems und ihre praktische Bedeutung, Leipzig, Georg Thieme, 1931 (g) Aschoff, cited by Lampert^{30f} (h) Vulpain (1873), cited by Rosenthal³¹

31 Mantegazza² Zahn³ Bizzozero⁴ Jones⁵ Osler⁶ Hayem⁷ Aynaud^{9c} Fonio and Schwendener^{9f}

32 Bizzozero⁴ Hayem⁷ Schimmelbusch⁸¹

33 Zahn³ Hayem⁷

34 (a) Solandt, D Y, and Best, C H Time-Relations of Heparin Action on Blood-Clotting and Platelet Agglutination, *Lancet* **1** 1042, 1940 (b) Shionoya, T Studies in Experimental Extracorporeal Thrombosis III Effects of Certain Anticoagulants (Heparin and Hirudin) on Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, *J Exper Med* **46** 19, 1927

35 (a) Fonio and Schwendener^{9f} (b) Quick, A J Studies on the Enigma of the Hemostatic Dysfunction of Hemophilia, *Am J M Sc* **214** 272, 1947 (c) Eagle, H Recent Advances in the Blood Coagulation Problem, *Medicine* **16** 95, 1937 (d) Ferguson, cited by Eagle^{35c} (e) Bessis, M, and Burnstein, M Études sur la physiologie des thrombocytes (Revue generale et travaux personnels), *Rev d'hemat* **3** 69, 1948

thrombin much too small to catalyze the conversion of fibrinogen into fibrin have been found sufficient to affect platelets *in vitro*³⁶ Quick^{35b} postulated the occurrence during clotting of a chain reaction in which lysis, initiated by minute amounts of thrombin, liberates enzymic material from platelets, the material, in turn, catalyzes the formation of active thromboplastin from a precursor of thromboplastin in plasma, resulting in the very rapid conversion of prothrombin into thrombin. The concept of a chain reaction involving thrombin formation explains rather effectively the accelerating effect of blood platelets on blood coagulation³⁶ as well as their rapid agglutination and lysis in large numbers during the same process.

ROLE OF ENDOTHELIAL CHANGES IN THROMBOSIS

Since Virchow's time, most writers on the subject of thrombosis have accepted the theory that three factors are involved: (1) changes in the composition of the circulating blood, such as increased coagulability or increased platelet count and agglutinability, (2) injury of the vessel wall, which results in the liberation of thromboplastin from tissue or favors the deposition of platelets on an altered surface, and (3) abnormalities of blood flow, which favor the coagulation of blood or the sedimentation of platelets. The evidence which incriminates endothelial injury has been largely experimental, such as the induction of thrombosis by injury (mechanical,³⁷ chemical³⁸ or thermal³⁹) of either the

36 (a) Milstone, J. H. Activation of Prothrombin by Platelets Plus Globulin, *Proc Soc Exper Biol & Med* **68** 225, 1948. (b) Ware, A. G., Fahey, J. L., and Seegers, W. H. Platelet Extracts, Fibrin Formation and Interaction of Purified Prothrombin and Thromboplastin, *Am J Physiol* **154** 140, 1948. (c) Eagle, H. Studies on Blood Coagulation. I. The Role of Prothrombin and of Platelets in the Formation of Thrombin, *J Gen Physiol* **18** 531, 1935.

37 (a) Mantegazza² (b) Zahn³ (c) Bizzozero⁴ (d) Jones⁵ (e) Hirsch, E., and Loewe, L. A Method for Producing Experimental Venous Thrombosis, *Proc Soc Exper Biol & Med* **63** 569, 1946. (f) Hayem, G. *L'Hématoblaste troisième élément du sang*, Paris, Presses Universitaires de France, 1923. (g) Rabinovitch, J., and Pines, B. The Effect of Heparin on Experimentally Produced Venous Thrombosis, *Surgery* **14** 669, 1943. (h) Murray, D. W. G., Jaques, L. B., Perrett, T. S., and Best, C. H. Heparin and the Thrombosis of Veins Following Injury, *ibid* **2** 163, 1937. (i) Morton, C. B., Shearburn, E. W., and Burger, R. E. Synthetic Vitamin K and the Thrombosis of Veins Following Injury, *ibid* **14** 915, 1943. (j) Kristenson, A. Beobachtungen über die Anzahl der Thrombozyten bei experimentell an Kaninchen hervorgerufener Thrombose, *Acta med Scandinav* **70** 167, 1929.

38 (a) Zahn³ (b) Jones⁵ (c) Murray^{37h} (d) Moses, C. An Evaluation of the Effect of Stasis in the Production of Experimental Thrombosis, *Federation Proc* **4** 52, 1945. The Effect of Heparin and Dicoumarol on Thrombosis Induced in the Presence of Venous Stasis, *Proc Soc Exper Biol & Med* **59** 25, 1945. (e) Hueper, W. C. Experimental Studies in Cardiovascular Pathology. X. Effects

entire wall or the intima or adventitia alone,⁴⁰ or the insertion through the wall into the lumen of foreign objects such as threads of fiber⁴¹ or metal,⁴² or metal, glass or collodion cannulas⁴³ Platelet thrombi generally appeared within a short time Apitz^{10a} reported early stages of thrombus formation occurring as quickly as five minutes after the daubing of the outer wall of the vein of a rabbit with alcohol Evidence of inflammation and even a coating of fibrin or other exudate were lacking at this stage

The nature of thrombosis has been thought to be noninflammatory in the majority of cases in man studied by a number of observers⁴⁴ Aschoff^{8d} could find no well authenticated cases in the literature in

of Repeated Intravenous Injections of Solutions of Digitonin on the Blood and the Internal Organs of Dogs and Rabbits, Arch Path **38** 326 (Nov) 1944 (f) Solandt, D Y, and Best, C H Heparin and Coronary Thrombosis in Experimental Animals, Lancet **2** 130, 1938 (g) Kojima, S Experimentelle Untersuchungen über Veränderungen des Blutes durch aseptische Thrombenbildung, Arch f klin Chir **174** 216, 1933

39 Zahn⁸ Eberth and Schimmelbusch^{8b} Fonio, A, and Vannotti, A Neuere Untersuchungen über die Entstehung der Thrombose, Schweiz med Wchnschr **64** 1086, 1934

40 Zahn⁸ Bizzozero⁴ Eberth and Schimmelbusch^{8b} Apitz^{10a} Solandt and Best^{8ef} Dietrich, A Gefasswand und Thrombose, Verhandl d deutsch Gesellsch f Kreislaufforsch, 1934, p 48

41 Mantegazza² Zahn⁸ Bizzozero⁴ Osler⁶ Eberth and Schimmelbusch^{8b} Hayem^{8ff} Zurhelle, E Experimentelle Untersuchungen über die Beziehungen der Infektion und der Fibringerinnung zur Thrombenbildung im stromenden Blut, Beitr z path Anat u z allg Path **47** 539, 1910

42 Zahn⁸ Hayem^{8ff}

43 (a) Best, Cowan and Maclean^{10b} (b) Dale and Jaques^{10d} (c) Rowntree L G, and Shonoya, T Studies in Experimental Extracorporeal Thrombosis I A Method for the Direct Observation of Extracorporeal Thrombus Formation, J Exper Med **46** 7, 1927 (d) Bollman, J L, and Preston, F W The Effects of Experimental Administration of Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin), J A M A **120** 1021 (Nov 28) 1942 (e) Murray, G, and Janes, J M Prevention of Acute Failure of Circulation Following Injury to Large Arteries Experiments with Glass Cannulas Kept Patent by Administration of Heparin, Brit M J **2** 6, 1940

44 (a) Jorpes, J E Heparin in the Treatment of Thrombosis An Account of Its Chemistry, Physiology and Application in Medicine, ed. 2, London, Oxford University Press, 1946 (b) Hunter, W C, Krygier, J J, Kennedy, J C, and Sneed, V D Etiology and Prevention of Thrombosis of the Deep Leg Veins A Study of Four Hundred Cases, Surgery **17** 178, 1945 (c) Lenggenhager, K Ueber die Entstehung, Erkennung und Vermeidung der postoperativen Fernthrombose, Leipzig, Georg Thieme, 1941 (d) Murray, G, and MacKenzie, R Postoperative Thrombosis and Embolism, Am J Surg **57** 414, 1942 (e) von Seemen, H, and Binswanger, H Ueber Allgemeinveränderungen, besonders des Blutes, nach chirurgischen Eingriffen und ihre Bedeutung für Entstehung und Bekämpfung der mittelbaren Operationsschädigungen, Deutsche Ztschr f Chir **209** 157, 1928

which thrombosis had really been brought about by changes in the endothelium, like many others he regarded physical factors (particularly sluggish blood flow and local eddy formation) as chief in importance

Although histologic changes in endothelium may not be demonstrable, the possibility cannot be rejected that a physiochemical change is the basic local occurrence which cause platelets to adhere. As previously mentioned, platelet adhesion outside the body is determined by the presence of a wettable surface of glass or other material. The importance of wettability appears to lie chiefly in the fact that thrombin, which is probably necessary for initiating platelet adhesion and lysis as well as for blood clotting, can be produced from the interaction of a wettable surface and plasma even when the latter is practically platelet free⁴⁵. Therefore, in order to explain thrombosis, it is necessary to postulate merely the development of wettability in the endothelium regardless of its normally maintained histologic appearance. The susceptibility of platelets to minute quantities of thrombin renders them a highly sensitive indicator of such endothelial change. The immunity of the intact, healthy subject to the spontaneous formation of platelet thrombi argues for the relative "nonwettability" of normal endothelium throughout the body. The concept of a "lack of adhesion" of the vascular lining was proposed by Freund⁴⁶ (1886) to explain the normal absence of clotting within living blood vessels as well as their failure to be stained by their contained blood. According to Clark,⁴⁷ the endothelium provides an extremely smooth lining to the whole of the cardiovascular system, minimizing friction in the flow of the blood and, in the smaller vessels, allowing the corpuscles to slip easily along its surface with no tendency to adhere. This character changes rapidly in response to any injurious stimulus (Clark and Clark⁴⁸). If, for example, capillary endothelium is exposed to heat or to chemical irritants or receives mechanical injury, it becomes rather swollen and sticky, so that the corpuscles cling to its surface. In an extended study of the surface activity of a wide range of nonvital materials, including many which had water-repellent properties, Lampert³⁰¹ concluded that

45 (a) Aynaud^{9c} (b) Lozner, E. L., Taylor, F. H. L., and MacDonald, H. Effect of Foreign Surfaces on Blood Coagulation, *J. Physiol.* **21** 241, 1942 (c) Nolf, cited by Lozner and others^{45b} (d) Ferguson, J. H. A New Blood-Clotting Theory, *Science* **97** 319, 1943 (e) Lenggenhager, K. Irrwege der Blutgerinnungsforschung, *Klin. Wchnschr.* **15** 1835, 1936

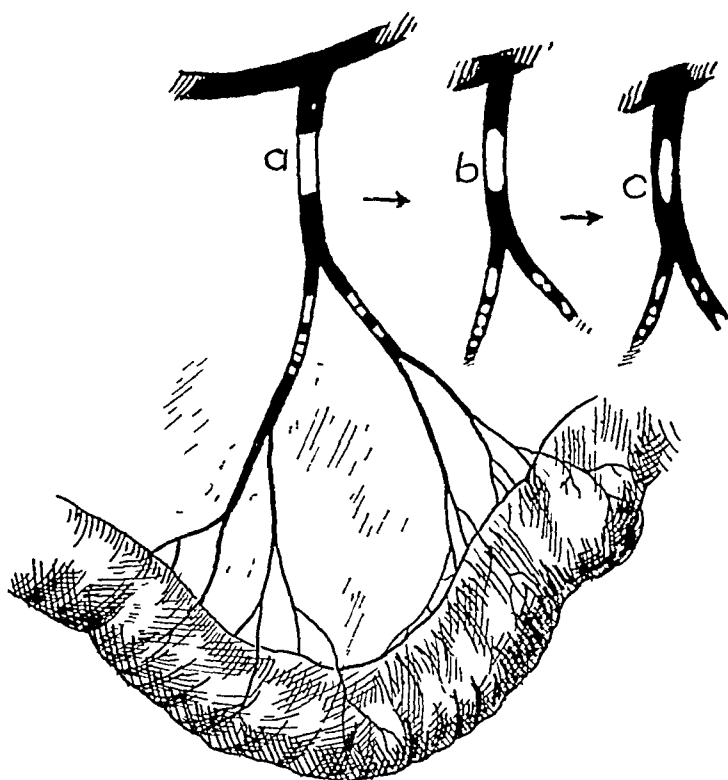
46 Freund, E. Ein Beitrag zur Kenntniss der Blutgerinnung, *Med. Jahrb.* **1** 46, 1886

47 Clark, W. E. Le Gros. *The Tissues of the Body*, ed. 2, Oxford, Clarendon Press, 1945, p. 168

48 Clark, E. R., and Clark, E. L. Observations on Changes in Blood Vascular Endothelium in the Living Animal, *Am. J. Anat.* **57** 385, 1935

the rate of blood clotting and that of platelet attraction toward a particular type of surface were specifically related to its wettability. On the basis of his observations, he postulated a relation between endothelial wettability and the formation of white thrombi.

The development of wettability of endothelium can be readily demonstrated in the animal by a simple experiment.⁴⁹ Through a fine needle, a small bubble of air is introduced into one of the veins of a rabbit mesentery immediately after the animal has been killed and its abdominal cavity exposed. At first, the interface between blood and air appears as a very slightly concave meniscus. Within a short time the inter-



Development of endothelial wettability following cessation of circulation, as indicated by the formation of a concave meniscus between the blood and the air. *a*, Appearance of an air segment in a mesenteric vein shortly after the death of an experimental animal, *b*, eighteen minutes after death, *c*, forty-five minutes after death (sketch from actual experiment, showing how the initial slight concavity of the meniscus between blood and air is masked when in the direct line of vision but becomes clearly defined as the film of blood advances along the uncovered endothelium with increasing wettability).

face becomes more deeply concave, indicating thereby the progressive change from a relatively nonwetttable endothelium to a highly wettable endothelium, as shown in the illustration. The experiment can be paralleled in nonvital materials by drawing blood into two narrow glass capillary tubes, one of which has been made nonwetttable with paraffin or silicone, in the treated tube the upper end of the column

49 Moolten, S. E., and Vroman, L. Unpublished data, 1948.

of blood is seen to be a flat meniscus, in contrast to the concave meniscus formed by blood in ordinary glass. In addition, a striking lack of friction in the inflow and outflow of blood can be demonstrated in the nonwettable tube when compared with the other.

The relative nonwettability of healthy endothelium, which is important in maintaining a frictionless inner lining of blood vessels as well as a fluid condition of the blood itself, may therefore be postulated as an actively vital property of endothelial cells in general and as probably dependent, as such, on the adequacy of their nutrition and organization. Accordingly, factors which affect the nutrition of the inner layers of blood vessels, impairing their vitality and causing endothelium to lose its physiologic nonwettability, may rightfully be regarded as the basic local determinants of thrombus formation. Chief among these factors is arteriosclerosis (more particularly, atheroma) which is rarely lacking when thrombosis appears in a coronary or cerebral artery or in one in a limb⁵⁰. Damage to the endothelium covering an atheromatous plaque, either calcified or distended with old or recent hemorrhage, is partly the result of mechanical injury and partly due to loss of the normal intimal cushion which ordinarily protects and nourishes the lining cells. In the lower extremities, calcification of the media may play a part in causing intimal damage and thrombosis, possibly through simple mechanical interference with nutrition of the inner layers⁵¹. A similar mechanism may underlie thrombosis following prolonged external compression of an artery by a cervical rib,⁵² by the use of a crutch⁵³ or by the habitual crossing of the legs over the knees⁵⁴. Prolonged vasospasm, curtailing the flow of nutrients from adventitial vessels through the tightly contracted media, appears to be a decisive contributing factor in the progress of organic changes in the intima in peripheral vascular disease,

50 (a) Allen, E. V., Barker, N. W., and Hines, E. A., Jr. *Peripheral Vascular Diseases*, Philadelphia, W. B. Saunders Company, 1946. (b) Paterson, J. C. Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, *Arch. Path.* **25** 474 (April) 1938. (c) Horn, H., and Finkelstein, L. E. Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion, *Am. Heart J.* **19** 655, 1940. (d) Wright, I. S., and Foley, W. T. Use of Anticoagulants in the Treatment of Heart Disease, with Special Reference to Coronary Thrombosis, Rheumatic Heart Disease with Thromboembolic Complications and Subacute Bacterial Endocarditis, *Am. J. Med.* **3** 718, 1947. (e) Graef, I., cited by Wright and Foley^{50d}. (f) Aring, C. D., and Merritt, H. H. Differential Diagnosis Between Cerebral Hemorrhage and Cerebral Thrombosis. A Clinical and Pathologic Study of Two Hundred and Forty-Five Cases. *Arch. Int. Med.* **56** 435 (Sept.) 1935.

51 Personal observation.

52 Allen, Barker and Hines^{50a}.

53 Platt, H. Occlusion of the Axillary Artery Due to Pressure by a Crutch. Report of Two Cases, *Arch. Surg.* **20** 314 (Feb.) 1930.

54 London, I. M. Personal communication to the authors.

such as thromboangitis obliterans and arteriosclerosis,⁵⁵ as well as in such definitive vasospastic disorders as Raynaud's disease⁵⁶ and ergotism,^{55c} and may well be the critical factor in precipitating thrombosis in all these conditions. Similar mechanisms may be involved in the thromboses of frostbite.⁵⁷ Pressure on the deep veins of the legs during prolonged recumbency on a firm mattress has been charged with principal responsibility for phlebothrombosis following operations.⁵⁸

The etiologic principles concerned in arterial and venous thrombosis can be extended to explain the formation of large mural ventricular thrombi in cases of myocardial infarction.⁵⁹ These constitute one of the chief causes of serious or fatal issue in the wake of the acute attack. Mural thrombi of the ventricles may result from various other inflammatory and degenerative lesions of heart muscle, such as Fiedler's myocarditis⁶⁰ and idiopathic cardiac hypertrophy of adults.⁶¹ Similar factors are concerned also in the formation of mural thrombi of the atriums and atrial appendages in which conditions of flow are such

55 (a) Bernheim, A. R., and London, I. M. Arteriosclerosis and Thrombo-Angitis Obliterans. Report of Cases and Treatment, *J. A. M. A.* **108** 2102 (June 19) 1937. (b) Hueper, W. C. Arteriosclerosis, *Arch. Path.* **38** 245 (Oct.) 1944, (c) p. 278.

56 Lewis, T., and Pickering, G. W. Observations on Maladies in Which Blood Supply to Digits Ceases Intermittently or Permanently and on Bilateral Gangrene of Digits. Observations Relevant to So-Called "Raynaud's Disease," *Clin. Sc.* **1** 327, 1934.

57 Lange, K., and Boyd, L. J. Use of Fluorescein Method in Establishment of Diagnosis and Prognosis of Peripheral Vascular Diseases, *Arch. Int. Med.* **74** 175 (Sept.) 1944, *Science* **102** 151, 1945.

58 (a) Rossle, R. Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, *Virchows Arch. f. path. Anat.* **300** 180, 1937. (b) Frykholm, R. The Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis, *Surg., Gynec. & Obst.* **71** 307, 1940.

59 Welch^{8c} Solandt, D. Y., Nassim, R., and Best, C. H. Production and Prevention of Cardiac Mural Thrombosis in Dogs, *Lancet* **2** 592, 1939. Nay, R. M., and Barnes, A. R. Incidence of Embolic or Thrombotic Processes During Immediate Convalescence from Acute Myocardial Infarction, *Am. Heart J.* **30** 65, 1945. Hellerstein, H. K., and Martin, J. W. Incidence of Thrombo-Embolic Lesions Accompanying Myocardial Infarction, *ibid.* **33** 443, 1947.

60 Fiedler, A. Ueber akute interstitielle Myokarditis, *Centralbl. f. inn. Med.* **21** 212, 1900. Scott, R. W., and Saphir, O. Acute Isolated Myocarditis, *Am. Heart J.* **5** 129, 1929. de la Chapelle, C. E., and Graef, I. Acute Isolated Myocarditis, with Report of Case, *Arch. Int. Med.*, **47** 942 (June) 1931.

61 Levy, R. L., and Rousselot, L. M. Cardiac Hypertrophy of Unknown Etiology in Young Adults, *Am. Heart J.* **9** 178, 1933. Dock, W. Marked Cardiac Hypertrophy and Mural Thrombosis in the Ventricles in Beriberi Heart, *Tr. A. Am. Physicians* **55** 61, 1940. Smith, J. J., and Furth, J. Fibrosis of the Endocardium and the Myocardium with Mural Thrombosis. Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart, *Arch. Int. Med.* **71** 602 (May) 1943.

that massive red thrombi may result, this is particularly true in severe mitral stenosis, in which the left atrium may become completely occluded^{8c}

Nonbacterial thromboendocarditis of varying types⁶² is probably determined by the same principles. When the vegetations occur on previously normal valvular endocardium, the wettability which favors such platelet deposition may be part of the endothelial component of diffuse mesenchymal disease or the result of advanced debility and cachexia.

The vegetations which are formed on the heart valves in bacterial endocarditis are composed principally of masses of platelets agglutinated about bacterial colonies⁶³. The platelet component, because of its bulk, constitutes a double hazard, increasing the size of emboli and shielding the micro-organisms from the action of antibacterial agents in the circulating blood. It is conceivable that a preparatory deposit of sticky platelets, accumulating on areas of wettable endocardium such as may develop on preexisting lesions of rheumatic endocarditis or congenital deformities of the valves or chambers, supplies the initial anchorage of such micro-organisms carried thence in the course of transient bacteremia.

The intravascular action of fat solvents and of detergent substances is logically explained in terms of their effect on the endothelium. Small amounts of dilute ethyl alcohol can be shown to increase endothelial wettability rapidly at the site of injection in a mesenteric vein prepared with an air bubble according to the technic described previously⁴⁹. The intravenous administration of ether has long been known to cause extensive thrombosis, beginning at the site of administration (Aschoff,^{30j} Lampert³⁰ⁱ). Saponins, such as digitonin, injected intravenously may produce thrombi at the site of injection as well as in distant vessels^{38e}. The presence of saponins in crude digitalis preparations may be responsible according to Hueper,^{38e} (possibly through their effects on endothelial wettability) for the increased incidence of thrombi after digitalis therapy reported by de Takats⁶⁴. It is unnecessary to invoke the hypothesis that such thrombi result from the thromboplastic action of digitalis, a hypothesis which has been disputed by a number of observers⁶⁵.

62 Gross, L., and Friedberg, C. K. Nonbacterial Thrombotic Endocarditis. Classification and General Description, *Arch Int Med* **58** 620 (Oct.) 1936

63 Osler⁶ Welch^{8c} Personal observation

64 de Takats, G., Trump, R. A., and Gilbert, N. C. The Effect of Digitalis on the Clotting Mechanism, *J. A. M. A.* **125** 840 (July 22) 1944

65 (a) Moses, C. The Effect of Digitalis, Epinephrine, and Surgery on the Response to Heparin, *J. Lab. & Clin. Med.* **30** 603, 1945. (b) Sokoloff, L., Ferrer, M. I., and DeGraff, A. C. The Effect of Digitalization on the Coagulation Time of the Blood in Man, *Federation Proc.* **4** 136, 1945

The foregoing description of the genesis of thrombosis may be epitomized in the following manner

1 The alteration of endothelial lining, even when not demonstrable histologically, may render it more wettable and initiate thereby the local production of thrombin

2 Platelets swept into contact with such altered endothelium adhere to it and are in turn made further agglutinable by the lytic action of locally formed thrombin, thereby entrapping other platelets in large numbers. As their lysis proceeds to completion the agglutinated platelets liberate accelerator substances which intensify the local production of thrombin. If the blood flow is rapid, much of the deposit of thrombin and platelets is swept away. If the current is relatively sluggish, platelets are deposited in rapidly mounting number until the lumen is totally occluded by white thrombus.

3 Continued elaboration of thrombin under the accelerating influence of platelet lysis en masse in the newly formed white thrombus quickly results in clotting of the entire column of stagnant blood above and below it to form a red thrombus. In a vein, the red thrombus, attached at first only to the sticky platelets comprising the white thrombus, may become dislodged as an embolus, especially after its retraction. Endothelial wettability may facilitate the latter process as indicated later in this report.

QUALITATIVE AND QUANTITATIVE VARIATIONS IN BLOOD PLATELETS

It is now generally appreciated that the varying susceptibility of individual subjects to thrombosis or to hemorrhage may be correlated, to a large extent, with differences in the characteristics of the blood platelets. Numerical differences are apparently overshadowed by qualitative differences, which can be demonstrated morphologically⁶⁶ or by technics for measuring the rate of platelet lysis⁶⁷ or agglutination⁶⁸

66 (a) Tocantins⁹⁸ (b) Rosenthal⁹¹ (c) Jurgens^{11d} (d) Frank^{12e} (e) Jurgens and Naumann^{18g} (f) Jurgens, R., and Graupner, H. Darstellung eines Entwicklungssystems der Thrombocyten. Zugleich ein Beitrag über das "Blutplättchenbild" der Blutkrankheiten, *Folia haemat* **57** 263, 1937. (g) Arneth, J. Ueber das qualitative (im engeren Sinne biologische) Verhalten der Blutplättchen bei der Perniciosa (qualitatives Thrombocytenblutbild), *ibid* **57** 1, 1937. (h) Ueber das qualitative Verhalten der Thrombocyten und Leukocyten bei der Hamophilie und bei der essentiellen Thrombopenie, *ibid* **57** 166, 1937. (i) Olef, I. The Differential Platelet Count. Its Clinical Significance, *Arch Int Med* **57** 1136 (June) 1936.

67 (a) Baar and Szekely^{18b} (b) Lee, P., and Erickson, B. N. Platelet Studies in Normal Men and Women (Menstruating and Nonmenstruating) and Subjects with Bleeding Disorders, *J Lab & Clin Med* **24** 821, 1939. (c) Olef, I. Rate of Disintegration of Platelets, *ibid* **22** 128, 1936, cited by Lee and

in vitro Platelets which appear defective morphologically or which lack the capacity of becoming readily agglutinated tend to be inefficient in arresting hemorrhage despite their presence in normal numbers⁶⁹ Such platelets are characteristic of purpura hemorrhagica associated with splenic hypertrophy ("hypersplenism")⁷⁰ After splenectomy and coincident with cessation of the bleeding tendency they may no longer be observed, even in cases in which the total platelet count returns to the previous low level⁷¹ Conversely, the increased capacity of platelets to agglutinate or adhere often coincides with an increased tendency to thrombosis and to shortened bleeding time Such an increase in platelet agglutinability and adhesiveness has been noted with fair

Erickson^{67b} (d) Muhrer, M, Bogart, R, and Hogan, A Estimation of Platelet Fragility, *Am J Physiol* **141** 449, 1944 (e) Tocantins, L M, Technical Methods for the Study for the Blood Platelets A Critical Review with Bibliography, *Arch Path* **23** 850 (June) 1937

68 (a) Jurgens and Naumann^{13g} (b) von Seemen and Binswanger^{44e} (c) Øllgaard, E On the Agglutination of the Blood Platelets Under Normal and Pathological Conditions, *Acta med Scandinav* **115** 1, 1943 (d) Copley, A L, and Robb, T P Studies on Platelets III The Effect of Heparin in Vivo on the Platelet Count in Mice and Dogs, *Am J Clin Path* **12** 563, 1942 (e) Copley, A L Embolization of Platelet Agglutination Thrombi in the Hamster's Pouch Produced by Heparin, *Federation Proc* **7** 22, 1948 (f) Copley, A L, and Houlihan, R B On the Mechanism of Platelet Agglutination, *ibid* **4** 173, 1945

69 (a) Jurgens^{11d} (b) Frank^{12e} (c) Footnote 13 c, g and i (d) Brill, N E, and Rosenthal, N Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica), *Arch Int Med* **32** 939 (Dec) 1923 (e) Rosenthal, N Hemorrhagic Diatheses Thrombocytopenia, Thrombasthenia, Capillary (Hemorrhagic) Toxicosis, Hemophilia and Thrombocythemia, in Downey, H Handbook of Hematology, New York, Paul B Hoeber, Inc, 1938, vol 1, sect 8, p 501 (f) Uotila, U On Hemorrhagic Thrombocythemia, *Acta med Scandinav* **95** 136, 1938 (g) Epstein, E, and Goedel, A Hamorrhagische Thrombocythämie bei vascularer Schrumpfmilz, *Virchows Arch f path Anat* **292** 233, 1934 (h) Reid, J Haemorrhagic Thrombocythaemia, *Lancet* **2** 584, 1940 (i) Frank, E, Die hamorrhagischen Diathesen, in Schittenhelm, A Enzyklopadie der inneren Medizin (special part 10) Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol 2, p 289 (j) Bernard, J, and Soulier, J P Investigation of a New Variety of Congenital Hemorrhagic Thrombocytic Dystrophy, read before the International Society of Hematology, Buffalo, N Y, Aug 23, 1948

70 Jurgens^{11d} Baar^{13c} Jurgens and Naumann^{13g} Brill and Rosenthal^{69d}

71 (a) Jurgens^{11d} (b) Jurgens and Graupner^{66f} (c) Rosenthal, N, The Course and Treatment of Thrombopenic Purpura, *J A M A* **112** 101 (Jan 14) 1939 (d) Leschke, E, and Wittkower, E Die Werlhofsche Blutfleckenkrankheit (thrombopenische Purpura) Ein Beitrag zur Pathologie der Blutplättchen und Capillaren und zur Pathogenese der hamorrhagischen Diathese, *Ztschr f klin Med* **102** 649, 1925-1926

regularity after operations,⁷² after childbirth^{13d} and in convalescence from infectious diseases,³⁰¹ especially typhoid⁷³

THROMBOCYTOSIN AND THROMBOCYTOPEN

The experimental data of Aynaud^{9c} (1909) and others⁷⁴ indicate that platelet agglutination can readily be brought about in vitro and in vivo by the addition to blood of peptones, various colloids, fatty emulsions, saponin, bile salts and tissue juices expressed from muscle, from fascia and, especially, from adipose tissue^{9c} It is probable that auto-lyzing tissues, such as those of large cancers, bring about similar effects in vivo through activation or liberation of proteolytic and lipolytic enzymes

In 1944, one of us (S E M)⁷⁵ undertook to investigate various organic factors which influence the number of blood platelets in circulation A lipid substance was discovered which, when injected into normal rabbits or fed to human subjects with thrombopenia, proved to be highly effective in increasing the rate of production of blood platelets This factor, termed "thrombocytosin," was found in abundance in subcutaneous fat, in egg yolk and in lymph nodes It was virtually absent in brain tissue, liver, bone marrow and perirenal fat It was abundant in the spleen, although normally in smaller quantity than its physiologic antagonist, "thrombocytopen" The possibility that thrombocytosin is inactivated in the spleen was suggested by the observation of large amounts of thrombocytosin in the urine of a splenectomized subject in contrast to the much smaller amount in normal persons

Subsequent studies of thrombocytosin⁷⁶ disclosed the important fact that it also increases the adhesiveness of platelets in vitro and in the living animal In therapeutic trials, it was helpful in several cases of abnormal bleeding when given orally or by intramuscular injection Parallel with the reduced tendency to bleed, a rise occurred in the platelet count and in the platelet adhesiveness, which was measured

72 (a) Jurgens^{11d} (b) Wright^{13d} (c) Starlinger and Sametnik²⁸ (d) von Seemen and Binswanger^{44e} (e) Olef⁶⁶¹ (f) Øllgaard^{68c} (g) Mackay, W The Blood Platelet Its Clinical Significance, Quart J Med **24** 285, 1931

73 Hartmann, E Ueber das Verhalten der Blutplättchen beim Typhus abdominalis, Deutsches Arch f klin Med **158** 1, 1927

74 (a) Tocantins^{9g} (b) Quick, A J, Ota, R K, and Baronofsky, I D On the Thrombopenia of Anaphylactic and Peptone Shock, Am J Physiol **145** 273, 1946

75 Moolten, S E Studies on Extractable Factors in the Spleen and Other Organic Sources Which Influence the Blood Platelet Count, J Mt Sinai Hosp **12** 866, 1945

76 Moolten, S E, and Vroman, L Unpublished data, 1947-1948

by the glass wool filter method, as described in the section on that technic. In 1 case of thrombopenic purpura, a single dose of 50 mg given parenterally reduced the bleeding time (Ivy method) from more than thirty minutes to six and three-quarters minutes, in another case it was reduced from over thirty-five minutes to four and one-half minutes. In a third case, that of a girl of 15, in which purpura was manifested chiefly as severe and protracted menorrhagia, thrombocytosis given prior to the onset of menses resulted in a normal flow lasting four to five days. It also alleviated, at least temporarily, the gingival bleeding of a patient with monocytic leukemia.

The existence of thrombocytosis was foreshadowed in the studies of Kugelmass,⁷⁷ who showed that a diet high in fat and protein in cases of thrombopenic purpura causes the blood platelet count to rise from low to normal, with the simultaneous disappearance of the hemorrhagic tendency. Similar findings were reported by Schiff and Hirschberger,⁷⁸ using egg yolk or sesame oil. They predicated the occurrence in these materials of a specific thrombocytosis-producing factor, the "fat-soluble T factor," although they did not isolate it. Acting on Kugelmass' evidence, Bancroft⁷⁹ employed a low fat, low protein diet in the prophylaxis of thromboembolism in surgical patients.

Among the many causes of increased platelet count, trauma to tissues (conspicuously laparotomy and fracture of the thigh), has been regarded as particularly significant.⁸⁰ The peak of postoperative thrombocytosis is generally recorded as being reached during the second week and has been stated to coincide approximately with the time of the greatest incidence of thromboembolism.⁸¹ The increase in plate-

77 Kugelmass, I. N. Clinical Control of Chronic Hemorrhagic States in Childhood, *J. A. M. A.* (Jan 20, 1934), "Bleeding" and "Clotting" Diets, *M. Clin. North America* **19** 989, 1935.

78 Schiff, E., and Hirschberger, C. Thrombocytosis Produced by a Hitherto Unknown Substance—the "Fat-Soluble T Factor," *Am. J. Dis. Child.* **53** 32 (Jan., pt. 1) 1937, *Ueber den T-Faktor*, *Jahrb. f. Kinderh.* **150** 247, 1937.

79 Bancroft, F. W., Stanley-Brown, M., and Chargaff, E. Postoperative Thrombosis and Embolism, *Ann. Surg.* **106** 868, 1937.

80 (a) Dawbarn, R. Y., Earlam, F., and Evans, W. H. The Relation of the Blood Platelets to Thrombosis After Operation and Parturition, *J. Path. & Bact.* **31** 833, 1928. (b) Hueck and Galloway, cited by Tocantins.⁹⁸ (c) König, W. Experimentelle Untersuchungen über die Entstehung der Thrombose. Ein Beitrag zur Lehre von den Blutplättchen, *Arch. f. klin. Chir.* **171** 447, 1932. (d) Adams, E. Postoperative Thrombocytosis, *Arch. Int. Med.* **73** 329 (April) 1944. (e) Wright, H. P. Changes in Numbers of Circulating Blood Platelets Following Experimental Traumatization, *J. Obst. & Gynaec. Brit. Emp.* **52** 253, 1945. (f) Evans, W. I., and Fowler, W. M. Effect of Splenectomy and Other Operative Procedures on Platelets as Determined Volumetrically, *Proc. Soc. Exper. Biol. & Med.* **32** 512, 1934.

81 Dawbarn, Earlam and Evans^{80a} Adams^{80d}

lets has been attributed to specific products of the breakdown of tissue which stimulate the activity of megakaryocytes, for example, products of nuclear breakdown^{80c} or, as previously suggested by one of us (S E M),⁷⁵ thrombocytosin mobilized from traumatized fat cells. Thrombocytosis of similar or much greater degree has been provoked by a variety of factors having in common a solvent or lytic action on adipose tissue, e g, irritation of the skin by ultraviolet light, iodine or generalized dermatoses⁸² and injections of turpentine,⁸³ saponin,⁸³ pyridine,²⁴ pyrodine (acetyl phenylhydrazine)⁸⁴ or lecithin⁸⁵

The sustained thrombocytosis, often reaching levels well above 1,000,000 platelets, which is encountered regularly after splenectomy is regarded by many as a release phenomenon occasioned by removal of a normal suppressive influence⁸⁶ rather than by a primary stimulation of the marrow

Thrombocytopen, a lipid substance found in the normal spleen,⁷⁵ is greatly increased in amount in the spleen of idiopathic purpura hemorrhagica,⁷⁵ from which it was originally extracted in crude form by Troland and Lee⁸⁷. On the other hand, in thrombopenia caused by bone marrow insufficiency, such as aplastic anemia or leukemia, splenic assay for thrombocytopen may show much less than the normal amount, particularly when the splenic pulp has become partly fibrous or has been replaced by leukemic cells⁷⁵. Although separated with difficulty from thrombocytosin because of many chemical and physical similarities, its biologic effects are almost completely opposite. As

82 (a) Steiner, P E, and Gunn, F D. The Response of Blood Platelets to External Stimuli. Ultraviolet Light, Iodine and Coal Tar, *Arch Path* **11** 241 (Feb) 1931. (b) Gunn, F D. Reactions of the Bone Marrow in Experimentally Induced Thrombocytosis, *ibid* **12** 153 (Aug) 1931.

83 Bunting, C H. Blood-Platelet and Megalokaryocyte Reactions in the Rabbit, *J Exper Med* **11** 541, 1909.

84 Mariconda, G. Osservazioni intorno alla origine istiocitaria delle piastrine del sangue, *Arch di fisiol* **32** 387, 1933. Ferrata and Rinaldo, cited by Gunn^{82b}. Frey, Jurgens and Bach, cited by Olef⁶⁶¹.

85 Ma, cited by Tocantins⁸⁵.

86 (a) Brill and Rosenthal^{69d}. (b) Frank,⁶⁹¹ (c) Lauda, E. Die normale und pathologische Physiologie der Milz, Berlin, Urban & Schwarzenberg, 1933. (d) Schousboe, J. Two Cases of Splenic Control of the Cell Emission from the Bone Marrow, *Acta med Scandinav* **103** 123, 1940. (e) Singer, K, Miller, E B, and Dameshek, W. Hematologic Changes Following Splenectomy in Man, with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, *Am J M Sc* **202** 171, 1941.

87 Troland, C, and Lee, F. A Preliminary Report on a Platelet-Reducing Substance in the Spleen of Thrombocytopenic Purpura, *Bull Johns Hopkins Hosp* **62** 85, 1938, Thrombocytopen. A Substance in the Extract from the Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces the Number of Blood Platelets, *J A M A* **111** 221 (July 16) 1938.

will be indicated later in this paper, thrombocytopen lowers the platelet count and platelet adhesiveness in the living subject and reduces platelet adhesiveness in vitro. After its administration in man, the proportion of large platelets is increased.⁷⁶ Although both thrombocytopen and thrombocytosis appear in the urine of normal persons, thrombocytopen is undetectable after splenectomy.⁷⁵

Thrombocytosis and thrombocytopen are, in effect, physiologic antagonists competing for a common substrate, the blood platelet and its parent megakaryocyte. For reasons which will be developed elsewhere in this paper, it appears reasonable to regard the unbalanced activity of either factor as an important element in the pathogenesis of either thromboembolic disease or idiopathic purpura.

OTHER FACTORS IN THROMBUS FORMATION

Emphasis on the importance of sluggish blood flow in thrombus formation received its impetus principally from the work of Virchow nearly a century ago and has become part of all orthodox teaching. The physical structure of white thrombi is believed to be determined largely by local mechanical conditions which govern the manner and rate of platelet deposition on endothelial surfaces so altered that platelet adhesion can occur. Von Recklinghausen⁸⁸ was among the first to appreciate the part played by local eddy currents in the blood stream, and Eberth and Schimmelbusch^{8b} soon offered experimental confirmation. The effect was described by Aschoff^{8d} as not unlike the silting up of sand along a breakwater or jetty in a slowly flowing river, an effect particularly noticeable on the outer surface of venous valves or in the bay of an abrupt widening of the lumen of a vessel just beyond a point of narrowing. The role of platelet "stickiness" as a necessary factor in this sandbank effect was studied experimentally by Lenggenhager,^{44c} employing thrombin-coated kaolin powder.

The significance of prolonged recumbency, on which a large body of current theory of thrombosis is based, has recently undergone reevaluation by Powers,⁸⁹ Blodgett and Beattie⁹⁰ and Allen, Linton and Donaldson.⁹¹ According to their clinical data the over-all incidence of postoperative thrombosis is not diminished by early postoperative

88 von Recklinghausen, cited by Eberth and Schimmelbusch^{8b} and Welch^{8c}

89 Powers, J. H. Postoperative Thromboembolism. Some Remarks on the Influence of Early Ambulation, *Am J Med* **3** 224, 1947

90 Blodgett, J. B., and Beattie, E. J. Early Postoperative Rising. A Statistical Study of Hospital Complications, *Surg, Gynec & Obst* **82** 485, 1946

91 (a) Allen, A. W., Linton, R. R., and Donaldson, G. A. Venous Thrombosis and Pulmonary Embolism, *J A M A* **133** 1268 (April 26) 1947. (b) Chapman, E. M., and Linton, R. R. Mode of Production of Pulmonary Emboli, *ibid* **129**:196 (Sept 15) 1945

rising but, if anything, may be increased, yet, the danger of fatal pulmonary embolism is appreciably lessened. The apparent paradox can easily be explained by the twofold origin of thrombi. Red thrombi, which constitute the principal element in embolism, can develop only in the presence of a complete standstill of circulation, such as follows venous occlusion by white thrombi, and owe their dangerous quality to the size they achieve through propagation in a quiet limb. White thrombi, on the other hand, can form only while circulation persists, however sluggishly, in order to provide a constant supply of fresh platelets for their continued growth. Evidences already given indicate that the white thrombus, to which basic guilt attaches in thrombotic disease, owes its size and rapidity of formation (1) to the number of sticky platelets available, (2) to endothelial wettability and (3) to conditions of flow which favor platelet agglutination to the vessel wall and to one another. Even rapid flow, as in the cardiac chambers, the aorta or the large arteries, does not necessarily prevent formation of white thrombus when other favoring influences exist.⁹²

Rossle,^{58a} Frykholm^{58b} and others⁹³ have drawn attention to the predominant origin of deep venous thrombi in the muscular twigs of the deep veins of the thighs and legs. In the opinion of the first two writers, a type of decubitus injury is caused in these vessels by the pressure of a firm mattress against the calf muscles or by that of the adductor muscles of the thighs against each other. Other factors may be the angulation of penetrating veins by side to side passive movements of calf muscles during dorsal recumbency and the activity of products of muscular degeneration resulting from prolonged inactivity and compression.^{58a} It remains to be tested whether or not thrombocytosis is also released by pressure atrophy of subcutaneous fat tissue in prolonged recumbency. Another factor deserving attention particularly in relation to endothelial wettability, is the phenomenon of "sludge" formation.⁹⁴

92 Osler⁶ Best, Cowan and Maclean^{10b} Rowntree and Shionoya^{40c} Murray and Janes^{48e} Gross and Friedberg⁶² De Santo, D. A. Operation and Trauma as a Cause of Coronary and Cerebral Thrombosis, *Am J Surg* **26** 35, 1934

93 (a) Hunter and others^{44b} (b) Homans, J. Venous Thrombosis in the Lower Limbs. Its Relationship to Pulmonary Embolism, *Am J Surg* **38** 316, 1937 (c) Bauer, G. Heparin Therapy in Acute Deep Venous Thrombosis, *J A M A* **131** 196 (May 18) 1946 (d) de Takats, G., and Fowler, E. F. The Problem of Thrombo-Embolism, *Surgery* **17** 153, 1945 (e) Ochsner, A. Venous Thrombosis, *J A M A* **132** 827 (Dec 7) 1946 (f) Neumann, R. Ursprungszentren und Entwicklungsformen der Benenthrombose, *Virchows Arch f path Anat* **301** 708, 1938

94 Knisely, M. H., Bloch, E. H., Eliot, T. S., and Warner, L. Sludged Blood, *Science* **106** 431 1947

PROPAGATION OF THROMBI

The formation of a massive thrombus by propagation from small thrombi within tributary twigs of the main venous channels of the leg or thigh has been explained^{8c, d} as the result of segmental formation of white thrombi wherever a vein filled with red thrombus joins another vein which is patent. In the latter vessel, freely flowing blood conveys fresh platelets past the projecting "tail" of red thrombus, which, being a site of active clotting, attracts and agglutinates platelets en masse. When the succeeding vessel has, in turn, become occluded by white thrombus, the thrombus again acts as a nucleus about which clotting occurs to form a new red thrombus up to the level of the next juncture and so on. It is commonly held today that phlebothrombosis of the lower extremities usually begins in the deep vessels of the calf and tends to propagate toward the heart. Thrombosis of the femoral vein, from which massive emboli spring, is thought to be rarely primary, contrary to older views including those of Aschoff,^{8d} but to represent an extension of smaller thrombi beginning in the legs or feet.⁹⁵

PRODUCTION OF EMBOLISM

Apparently little affinity exists between fibrin and the normal endothelial lining, hence long intravascular clots may easily be pulled out from veins.⁹⁴ It is obviously at this stage of development of the red thrombus that the risk of embolism is greatest. The duration of this stage, however, is generally no more than twenty-four to forty-eight hours.⁹⁶ Thereafter, the wall of the occluded vein becomes the seat of an aseptic inflammatory process which results in the fixation of red thrombus by organization, accompanied with tenderness and other local signs of inflammation.

Little is known of the possible determining factors in embolism. Mechanical influences, such as active movement of the limbs on getting out of bed, account in many instances for dislodgment of emboli. Straining movements in bed, which temporarily raise venous pressure and thus provoke a tidal recoil of venous blood, are held accountable by Chapman and Linton^{91b} for "bedpan deaths" from pulmonary embolism in bedridden patients. Nevertheless, the small proportion of emboli which actually arise in cases of venous thrombosis^{50a} compels one to search for some additional causative factor or factors. Hirschboeck and Coffey⁹⁷ drew attention to the role of clot retraction

95 Rossle^{58a} Footnote 93

96 Allen, Barker and Hines^{50a} Bauer^{93c}

97 (a) Hirschboeck, A. S., and Coffey, W. L., Jr. Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, *Am J M Sc* **205** 727, 1943. (b) Hirschboeck, J. S. Delayed Blood Coagulation and Absence of Clot Retraction in Collodion Lined Vessels, *Proc Soc Exper Biol & Med* **45** 122, 1940.

in the formation of emboli and reported pronounced shortening of clot retraction time in a high proportion of cases of pulmonary embolism. Formation of a protective blanket of serum about a red thrombus must obviously interfere with its attachment to the wall of the vein and facilitate its mobilization as an embolus. At least two factors are concerned in clot retraction ("syneresis") (1) the presence of blood platelets and (2) the nature of the surface of contact. The optimal retraction of clot in glass tubes requires an adequate number of intact qualitatively normal platelets (Tocantins⁹⁸). Postoperative thrombocytosis may accelerate clot retraction⁹⁹. Thrombin formation, especially the accelerated formation resulting from the catalytic activity of hyperadhesive platelets, may play a role, a possibility suggested by the discovery that a suspension of fine carbon particles (norit[®]) coated with thrombin can induce normal clot retraction in deplateletized plasma⁷⁶. On the other hand, clot retraction is inhibited by the contact of clotted blood with collodion surfaces (Hirschboeck^{97b}). In Lampert's opinion,³⁰¹ the most important factor in embolism is the quickening influence on clot retraction of pronounced wettability in the vessel wall. How endothelial wettability aids clot retraction is not altogether clear. Personal observations⁷⁶ of clotting blood on glass slides and on slides coated with water-repellent plastics suggest that the deciding element is rapid lysis of blood platelets in contact with a wettable surface, whereby fibrin filaments lose their means of attachment. In that event the role of endothelial wettability becomes doubly important, initiating platelet deposition as the mechanism of the white thrombus and favoring retraction of the red thrombus to increase the threat of embolism.

CHANGES IN THE CIRCULATING BLOOD SECONDARY TO THROMBUS FORMATION

Distinct lowering of the prothrombin level, measured by the one stage method (Quick), was observed shortly after thrombosis in some of our cases, but the level was not tested by the two stage method. It is possible that losses of prothrombin under these circumstances are quickly replaced, in contrast, a marked permanent loss of prothrombin (about 85 per cent, according to Quick^{35b}) occurs during clotting in the test tube.

98 Tocantins, L. M. Platelets and the Spontaneous Syneresis of Blood Clots, *Am J Physiol* **110** 278, 1934, Platelets and the Structure and Physical Properties of Blood Clots, *ibid* **114** 709, 1936.

99 Lampert³⁰¹ Hirschboeck and Coffey^{97a}

Increased clotting activity has been reported by a number of observers¹⁰⁰ in cases of thrombosis and has been adduced as evidence that the underlying cause of thrombosis is an increase in circulating thromboplastin and other clotting factors¹⁰¹ Ogura and his associates,^{100g} however, reported data from cases of coronary thrombosis which indicate that increased clotting activity (measured by a modified heparin tolerance test *in vitro*) follows rather than precedes coronary thrombosis and may therefore be the result of damage to myocardial tissue Shafiroff¹⁰² demonstrated that clotting activity in venous blood obtained from an extremity already affected by thrombosis was greater than that obtained from the opposite extremity

Our own observations in patients with thrombosis (to be described later in the paper) likewise suggest that increased clotting activity, measured by prothrombin time, clot retraction time^{97a} and heparin tolerance *in vitro*,^{100h} is not a primary cause of thrombosis but, rather, the secondary manifestation of the presence of a white thrombus As already stated, such a thrombus is composed principally of agglutinated platelets which undergo lysis and thereby accelerate the production of thrombin from precursor elements Quick^{35b} stated the belief that the normal platelet lysin is thrombin itself, evolved initially in minute amounts and evoking, thence, a chain reaction in which the

100 (a) Bancroft, Stanley-Brown and Chargaff⁷⁹ (b) Nygaard, K K, and Brown, G E Essential Thrombophilia Report of Five Cases, *Arch Int Med* **59** 82 (Jan) 1937 (c) Bergquist, G Ueber postoperative Thrombosen, *Acta chir Scandinav* **83** 415, 1940 (d) Brambel, C E, and Loker, F F Significance of Variations of Prothrombin Activity of Dilute Plasma, *Proc Soc Exper Biol & Med* **53** 218, 1943 (e) de Takats, G Heparin Tolerance A Test of the Clotting Mechanism, *Surg, Gynec & Obst* **77** 31, 1943 (f) Shapiro, S Hyperprothrombinemia A Premonitory Sign of Thromboembolization (Description of a Method), *Exper Med & Surg* **2** 103, 1944 (g) Ogura, J H, Fetter, N R, Blankenhorn, M A, and Glueck, H I Changes in Blood Coagulation Following Coronary Thrombosis Measured by Heparin Retarded Clotting Test (Waugh and Ruddick Test), *J Clin Investigation* **25** 586, 1946 (h) Tuft, H S, and Rosenfield, R E Detection of Intravascular Clotting Tendency by Heparin Tolerance Principle Methods and Clinical Application, *Am J Clin Path* **17** 862, 1947 (i) Kadish, A H Coagulation of the Blood in Lusteroid Tubes A Study of Normal Persons and Patients with Arterial or Venous Thrombosis, *Am Heart J* **34** 212, 1947 (j) Vander Meer, Newman and Wright Unpublished data, cited by Wright and Foley^{50d}

101 (a) Bancroft, Stanley-Brown and Chargaff⁷⁹ (b) Ogura and others^{100g} Tuft and Rosenfield^{100h} (c) de Takats and Fowler^{93d} (d) Ochsner^{93e} (e) Shapiro, S, Sherwin, B, and Gordimer, H Postoperative Thromboembolization The Platelet Count and the Prothrombin Time After Surgical Operations, A Simple Method for Detecting Reductions and Elevations of Prothrombin Concentration (or Activity) of the Blood Plasma, *Ann Surg* **116**.175, 1942

102 Shafiroff, B G P, Doubilet, H, Barcham, I S, and Co Tui The Coagulability of Venous Blood of Normal and Diseased Legs A Study of One Hundred Ninety-One Subjects, *Ann Surg* **118** 482, 1943

platelets occupy a leading role. Platelets in the process of lysis have also been shown to cause aged, inactive plasma to regain considerable clotting power (Roskam^{9m})

Accelerated platelet lysis, such as occurs in white thrombi, may explain the increased coagulability of the blood which has been reported to occur at the peak of the increase in platelets after operations,¹⁰³ after splenectomy,^{100h} after myocardial infarction^{100g} and during the platelet crises of essential thrombocythemia¹⁰⁴ or "essential thrombophilia"^{100b}, more specifically, increased coagulability has been reported in the venous return from a limb already harboring a thrombus¹⁰². Furthermore, thrombin which is formed about white thrombi is probably carried off into the general circulation as long as some flow persists past the site of origin and may also account to some extent for increased clotting activity and platelet lability.

In accordance with Quick's^{85b} postulate, as stated (that platelet lysis begets platelet lysis through the medium of accelerated thrombin formation), reduction in platelet lysis and, hence, in relative platelet adhesiveness during the administration of large doses of heparin sodium or dicumarol[®] may be explained as the direct result of an interruption of this chain reaction.

On the other hand, it should not be surprising if the rapid accumulation of large numbers of adhesive platelets as a localized white thrombus were to result in an absolute deficit of adhesive platelets in the circulating blood in the interval before the loss is replaced by regeneration. In actual experience, such rapid withdrawal of adhesive platelets from circulation can be demonstrated regularly during the formation of a large thrombus, particularly when platelet adhesiveness has been greatly increased beforehand, as in carcinoma. Thrombopenia secondary to thrombus formation in such cases may be extreme. This was seen, for example, in a patient dying of carcinoma of the stomach. In the last weeks of life, purpuric hemorrhages appeared in the skin and severe hemorrhage occurred from the carcinoma. The blood platelet count dropped to 147,000 per cubic millimeter and, later, to 62,000, with a pronounced decrease in adhesive platelets. The bleeding time became correspondingly prolonged (eleven and one-half to thirty-eight and one-half minutes). During that time, ischemic dry gangrene appeared in several toes, later followed by sudden hemiplegia and signs of pulmonary infarction. Massive thrombi were found at autopsy in the deep veins of the legs bilaterally, extending upward into the com-

103 Dawbarn, Earlam and Evans^{80a} Tuft and Rosenfield^{100h} Shapiro, Sherwin and Gordimer,^{101e}

104 Evans, W. H. The Blood Changes After Splenectomy in Splenic Anæmia, Purpura Hæmorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, *J. Path. & Bact.* **31** 815, 1928

mon iliac vessels, from which multiple pulmonary emboli and infarcts had arisen. The right auricular appendage was filled with mural thrombus. In addition, thrombotic vegetations were present on the cusps of the aortic valve (nonbacterial thromboendocarditis) and were presumed to be the source of emboli to the brain and to the toes.

THROMBOPENIA SECONDARY TO PLATELET AGGLUTINATION

Multiple emboli composed of agglutinated platelets, produced by a variety of causes, may be associated with a similar tendency to thrombopenia. Intravascular agglutination of platelets, which cannot be prevented with heparin sodium,^{74b} is reported to follow the intravenous injection of peptone and various colloids.¹⁰⁵ Intense but transitory thrombopenia accompanies this effect, which may result in purpura. Masses of agglutinated platelets plug the small vessels of many organs. Anaphylactic shock¹⁰⁶ and the injection of antiplatelet serum cause identical effects.¹⁰⁷ In man, multiple platelet thrombi of the minute vessels have been observed in fulminant purpura complicating meningococcus sepsis.¹⁰⁸ A rare but spectacular syndrome was also described by Moschcowitz¹⁰⁹; it is characterized by febrile anemia and the widespread formation of hyaline thrombi in minute vessels. Although in his case petechial hemorrhages were the only purpuric manifestation, subsequent case reports have listed marked thrombopenic purpura and, in some instances, a leukemoid picture. Baehr, Klemperer and Schiffrin¹¹⁰ pointed out the origin of these thrombi in platelets withdrawn in myriads from the circulating blood. Singer¹¹¹ proposed the name "thrombotic thrombocytopenic purpura" for this disorder, Fitzgerald¹¹² suggested the term "thrombocytic acroangiothrombosis" to indicate the localization of the thrombi in the terminal vessels.

105 Aynaud^{9c} Dameshek and Miller²²

106 Quick, Ota and Baronofsky^{74b} Biedl, A, and Kraus, R. Experimentelle Studien über Anaphylaxie, Wien klin Wchnschr **22** 363, 1909

107 Aynaud^{9c} Le Sourd and Pagniez, cited by Aynaud^{9c} Tocantins, L. M., and Stewart, H. L. Experimental Thrombopenic Purpura, Am J Path **15.1**, 1939

108 Hill, W. R., and Kinney, T. D. The Cutaneous Lesions in Acute Meningococcemia. A Clinical and Pathologic Study, J A M A **134** 513 (June 7) 1947

109 Moschcowitz, E. An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, Arch Int Med **36** 89 (July) 1925

110 Baehr, G., Klemperer, P., and Schiffrin, A. Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thrombosis of Capillaries and Arterioles, Tr Am Physicians **51** 43, 1936

111 Singer, K., Bornstein, F. P., and Wile, S. A. Thrombotic Thrombocytopenic Purpura, Blood **2** 542, 1947

112 Fitzgerald, P. J., Auerbach, O., and Frame, E. Thrombocytic Acroangiothrombosis (Platelet Thrombosis of the Capillaries, Arterioles, and Venules), Blood **2** 519, 1947

PREDICTION AND DIAGNOSIS OF THROMBOSIS BY LABORATORY METHODS

Coagulation Tests—The interest with which the problem of pre-clinical detection of thrombosis is regarded at present is reflected in the number and variety of tests which have been employed, although with inconstant success, in detecting the likelihood or actuality of thrombosis. The majority of these tests deal primarily with clotting factors, in accordance with the viewpoint that the underlying cause of thrombosis is an increase in circulating thromboplastin and in other elements concerned in the coagulation mechanism. According to certain writers, the coagulation time of whole blood^{100c} or plasma¹¹³ and the rate of conversion of prothrombin to thrombin are accelerated in patients manifesting a tendency to thrombosis. Shapiro^{100f} and Brambel and Loker^{100d} reported the existence of accelerated prothrombin time in diluted plasma, but this finding was not confirmed by Tuft and Rosenfield¹¹⁴. In most instances, prothrombin time has been measured in either whole or diluted plasma by the one stage method of Quick^{9k}. Several factors besides absolute amount of prothrombin may be involved in accelerated coagulation and in accelerated formation of thrombin^{100d}. These may include "accelerator globulin,"¹¹⁵ products of platelet lysis^{36a,b} (enzymic^{35b} or otherwise¹¹⁶), fibrinogen content^{9k} and tissue and plasma thromboplastins^{9k}. In general, these have been either ignored or included in the final result without specification.

The observation of increased heparin tolerance, as indicated by the coagulation time of blood taken after the intravenous administration of a standard test dose of heparin sodium (de Takats^{100e}), parallels the common finding that higher therapeutic dosages of heparin sodium are needed to produce prolongation of coagulation time during a thromboembolic episode than in the normal state. A modification of the test in vitro was devised by Waugh and Ruddick¹¹⁷ and further simplified by Tuft and Rosenfield^{100h}.

113 Bancroft, Stanley-Brown and Chargaff⁷⁹ Nygaard and Brown^{100b}

114 Tuft, H S, and Rosenfield, R E. Significance of the Accelerated Reaction in Determination of Prothrombin Time of Diluted Plasma, *Am J Clin Path* **17** 704, 1947

115 Ware, A G, Guest, M M, and Seegers, W H. A Factor in Plasma Which Accelerates the Activation of Prothrombin, *J Biol Chem* **169** 23, 1947
Ferguson, J H, and Lewis, J H. "Accelerator Globulin" and "Anti-Hemophilic Globulin" in Thrombin Formation from Aged Plasma and in Hemophilic Blood, *Proc Soc Exper Biol & Med* **67** 228, 1948

116 Roskam^{9m} Eagle^{36c}

117 Waugh, T R, and Ruddick, D W. A Test for Increased Coagulability of the Blood, *Canad M A J* **50** 547, 1944, Studies on Increased Coagulability of the Blood, *ibid* **51** 11, 1944

Not all observers are in agreement on the significance or reliability of these tests. Hurn, Barker and Mann¹¹⁸ found no known specific coagulation factor to be conclusively implicated in thromboembolic disease, confirming the findings of Ewing,¹¹⁹ Moses^{65a} and Potts and Pearl¹²⁰ Ogura,^{100g} who found coagulability to be increased after coronary thrombosis, regarded it as result and not as cause, although possibly important in the propagation of the initial thrombus and in the formation of mural thrombi. Even the latter is of doubtful consequence in view of the fact that thrombi can form in the presence of reduced coagulability as well.^{38d} The effectiveness of heparin sodium and dicumarol® in the prophylaxis and emergency treatment of thromboembolic disease depends primarily on a dosage sufficient to insure a pronounced reduction in clotting activity,¹²¹ probably to the point of reducing platelet adhesiveness as well.¹²²

Discrepancies in the observations just cited may possibly follow from the fact that no particularly decisive attempt has been made in most instances to correlate the laboratory data with the successive phases of thrombus development outlined previously. On the other hand, the fault may lie with the tests themselves. In a number of cases studied serially by us,¹²³ tests of platelet number and adhesiveness were made by a method to be described in this paper (the glass wool filter test) and simultaneous companion studies were made of prothrombin time, heparin tolerance in vitro^{100h} and clot retraction time.^{97a} In several of these cases, the results were consistent with clinical or other evidences which suggested developing or developed thrombosis. In other instances, the results of the coagulation tests were at variance with one another and with those of our own test. In general, coagulation tests proved less dependable than studies of blood platelets.

118 Hurn, M., Barker, N. W., and Mann, F. D. Variations in Prothrombin and Antithrombin in Patients with Thrombosing Tendencies, *Am J Clin Path* **17**:709, 1947.

119 Ewing, M. E., Cullimore, O. W., and Blatherwick, N. R. Plasma Clotting Time and Serum Calcium of Patients Recovered from Attacks of Coronary Thrombosis, *Proc Soc Exper Biol & Med* **47**:23, 1941.

120 Potts, W. J., and Pearl, E. A Study of the Platelet Count and the Coagulation Time of Plasma and Whole Blood Following Operation, *Surg, Gynec & Obst* **73**:492, 1941.

121 (a) Jorpes^{44a} (b) Allen, E. V. The Clinical Use of Anticoagulants. Report of Treatment with Dicumarol in 1,686 Postoperative Cases, *J A M A* **134**:323 (May 24) 1947.

122 Tocantins^{9g} Quick, A. J. The Anticoagulants Effective in Vivo with Special Reference to Heparin and Dicumarol, *Physiol Rev* **24**:297, 1944.

123 Moolten, S. E., and Vroman, L. The Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders. I. Measurement of Adhesiveness by the Glass-Wool Filter, *Am J Clin Path* **19**:701, 1949. Moolten, S. E., Vroman, L., Vroman, G. M. S. The Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders. II. Diagnostic and Prognostic Significance of Platelet Adhesiveness, *ibid* **19**:814, 1949.

Blood Platelet Counts—Several writers¹²⁴ have commented on the association of high platelet counts and the increased incidence of thromboembolism, either as a transient occurrence, after operation, post partum or otherwise, or as a persistent trait¹²⁵. Impressive examples of recurrent thrombosis related to chronically increased platelet formation may be encountered in certain cases of carcinoma (Trousseau's sign¹²⁶), of polycythemia vera¹²⁷ and of essential thrombocythemia¹²⁸. These conditions can perhaps best be considered together under the comprehensive title of "thrombophilia" (originally applied in cases of migratory thrombophlebitis¹²⁹). Many workers have been inclined to disregard the association between platelet count and thrombosis as no more than fortuitous¹³⁰ except in extreme instances or as incidental to some other, more basic factor¹³¹. Just as even severe thrombopenia may exist without an abnormal tendency to bleed (Macfarlane,¹⁷ Roskam,^{9m} Rosenthal^{69g}), so thrombocytosis of pronounced degree may occur without an increased tendency to thrombosis (Normann,¹³⁻ Adams^{80d} and others¹³³). On the other hand, a quick drop in the platelet count has been reported as a warning sign of thrombosis¹³⁴. Absence of the usual postoperative or postinfectious rise has been accorded similar significance^{80f}.

Tests of Platelet Agglutinability and Adhesiveness in Thromboembolism—Evidence has now accumulated in ample measure that a

124 Welch^{8c} Aschoff^{8d} Olef⁶⁶ⁱ Hartmann⁷³ Footnote 80 Tuft and Rosenfield^{100h} Shapiro, Sherwin and Gardiner^{101e}

125 (a) Olef⁶⁶ⁱ (b) Rosenthal⁶⁹ⁱ (c) Nygaard and Brown^{100b} (d) Rosenthal, N Clinical and Hematologic Studies on Banti's Disease I The Blood Platelet Factor with Reference to Splenectomy, J A M A **84** 1887 (June 20) 1925

126 Osler⁶ Cited by Welch^{8c} Hayem^{37f}

127 Rosenthal⁹¹ Olef⁶⁶ⁱ Norman, I L, and Allen, E V The Vascular Complications of Polycythemia, Am Heart J **13** 257, 1937

128 Rosenthal^{69g} Nygaard and Brown^{100b} Evans¹⁰⁴ Rosenthal^{125d}

129 Mendel, F Ueber "Thrombophilie" und das Fruhaufstehen der Wochnerinnen und Laparotomierten, Munchen med Wchnschr **56** 2149, 1909

130 (a) Allen, Barker and Hines^{50a} (b) Moses^{65a} (c) Potts and Pearl¹²⁰ (d) Windfeld, P Beitrage zur Kenntnis der postoperativen Blutveranderungen, Acta chir Scandinav (supp 25) **70** 1, 1933

131 Aschoff^{8d} Wright^{13d} Adams^{80d} Belt, T H Thrombosis and Pulmonary Embolism, Am J Path **10** 129, 1934

132 Normann, E Wie verhalten sich die Thrombocyten nach operativ behandelten Krankheitsfallen und bei der Entstehung postoperativer Thrombose? Deutsche Ztschr f Chir **212** 166, 1928

133 (a) Uotila^{69h} (b) Mackay^{72g} (c) Windfeld^{130d} (d) Di Guglielmo, G Eritroleucemia e piastrinemia, Folia med **6** 1, 36, 55, 81 and 101, 1920

134 (a) Kristenson^{37j} (b) Kojima^{38g} (c) Rosenthal^{125d} (d) Norman¹³² (e) Kristenson, A Beobachtungen uber die Thrombozytenzahl bei klinischer Venenthrombose, Acta med Scandinav **69** 453, 1928 (f) Woodruff, P The Behaviour of the Blood Platelets in Thyreotoxicosis, M J Australia **2** 190, 1940

relation exists between the increased stickiness of platelets and an abnormal susceptibility to thrombus formation. Von Seemen and Binswanger¹⁴⁶ were among the first to report an increase in platelet agglutinability in patients recovering from surgical procedures. They employed a method, devised by Burker¹³⁵ in 1903, which consisted in moist chamber observation of the platelets contained in plasma separating from a drop of finger blood collected in a paraffin cup to avoid clotting. According to them, platelets clumped in the greatest volume and speed three to six days after operation. A more elaborate method based on the same principle was devised by Jurgens and Naumann¹³⁷. Platelets were obtained in a suspension of plasma by permitting venous blood, unmixed with anticoagulant, to sediment quietly at refrigerator temperature in a paraffin-lined tube. Øllgaard^{68c} developed a macroscopic method in which platelet agglutinability was measured by determining the minimal amount of solution of mercuric chloride capable of producing visible flocculation of platelets suspended in citrated plasma and previously "stabilized" by being heated on a water bath at 42 C for three hours. In Copley's method,¹³⁶ platelets are stabilized by thorough washing in sodium chloride solution and are added to various plasmas for comparative macroscopic tests of agglutinability.

Platelet adhesiveness to a glass surface was measured by Morawitz and Jurgens¹³⁷ by determining the time required for a glass capillary tube to become plugged while blood was forced back and forth through it by means of a pumping device ("capillary thrombometer"). In a simpler and more reliable method, later devised by Wright,^{9a} platelet adhesiveness is calculated as the rate of loss of platelets from a measured sample of heparinized blood by their deposition on a glass surface. For this purpose she employed a specially designed, slowly rotating tube of glass, coated internally with paraffin, in which the specimen of blood is constantly passed over two small windows of uncoated glass during a period of eighty minutes. Platelet counts are made at intervals of twenty minutes.

Increased platelet agglutination has been encountered in a variety of clinical conditions. Øllgaard^{68c} found it increased, by his method, in many patients with acute febrile disease, in postoperative patients and in patients with thromboembolism. The administration of heparin sodium had an inhibitory effect. Morawitz and Jurgens¹³⁷ reported increased

135 Burker, K. Eine einfache Methode zur Gewinnung von Blutplättchen, *Centralbl f Physiol* **17** 137, 1903.

136 Footnote 68 *d*, *c* and *f*.

137 Morawitz, P, and Jurgens, R. Gibt es Thrombasthenie? *Muenchen med Wchnschr* **77** 2001, 1930, cited by Morawitz, P. Thrombose, *Verhandl d deutsch Gessellsch f Kreislaufforsch* 1930, **7** 80, 1934.

platelet adhesiveness in infections and in recurrent thrombosis which complicated polycythemia vera associated with hyperthrombocytosis, but not in ordinary "spontaneous" thrombosis. With the rotating tube, Wright^{13d} found adhesiveness regularly increased after operations and childbirth, paralleling in its rise and subsequent fall the curve of incidence of thromboembolism. The addition of anticoagulants to blood in vitro and the administration to human subjects of sufficient dicumarol® to produce hypoprothrombinemia brought about a significant lowering of platelet adhesiveness¹³⁸. By means of her method, Wright succeeded in translating into numerical units the principles of platelet adhesiveness which had been developed along various experimental lines, including the action thereon of anticoagulants, by Bizzozero⁴ (1882), Burkner^{9b} (1904), Deetjen^{9d} (1909), Shionoya^{34b} (1927), Best, Cowan and Maclean^{10b} (1938) and Dale and Jaques^{10d} (1942).

THE GLASS WOOL FILTER TEST

In the course of our primary studies on the action of thrombocytosis and thrombocytopen on blood platelets in vitro,⁷⁶ it was found necessary to improvise a test of platelet adhesiveness with which one could detect relatively small changes in this property. Glass wool (fiberglas®) was found to be serviceable in providing a maximum of glass surface for the blood sample being tested.

Procedure—In the standardized procedure followed at the time of this report,¹²⁸ glass wool is braided into a wick, cleansed with acetone, cut into a convenient length and inserted into the upper end of a test tube, from the mouth of which it is suspended freely by two arms of a Y made by splitting its upper part. The "filter" is moistened with sodium chloride solution, capped to prevent drying and brought to incubator temperature. Blood is drawn from a vein into a silicone-coated syringe containing sufficient sodium citrate to make a final concentration of 0.38 per cent. After a sample is removed for erythrocyte and platelet counts, 1 cc is taken up in a pipet, allowed to drip into the prepared filter (in which it is kept exactly thirty seconds) and then washed through with chilled sodium chloride solution containing 0.38 per cent sodium citrate. Erythrocyte and platelet counts are made from the filter washings and the results corrected for dilution against the prefiltration sample as a control. From these data, the number of platelets lost to the filter is easily computed and a factor is obtained for platelet adhesiveness ("adhesive index"). From this, the proportion of adhesive platelets can be computed with a simple formula. With the test properly standardized, a surprisingly stable level of adhesive platelets is found in normal persons, ranging between 60,000 and 110,000 adhesive platelets per cubic millimeter. In serial tests, the fluctuations within this range are normally of the same order as those of the total platelet count.

138 (a) Wright^{9b} (b) Spooner, M., and Meyer, O. O. The Effect of Dicumarol (3,3'-Methylenedis 4-Hydroxycoumarin) on Platelet Adhesiveness, *Am J Physiol* **142** 279, 1944 (c) Werner, M., Zeltmacher, K., Reich, C., and Shapiro, S. Platelet Adhesiveness, *Blood* **3** 1275, 1948

CLINICAL CORRELATIONS WITH INCREASED PLATELET ADHESIVENESS

The glass wool filter test for platelet adhesiveness was employed in a variety of clinical conditions in conjunction with other diagnostic procedures applicable to the study of thrombosis and of disorders of hemostasis. The results of the survey appear to strengthen the viewpoint that qualitative changes in the blood platelets have greater significance than numerical changes. Increased platelet adhesiveness was found to be an almost constant accompaniment of cellular destruction anywhere in the body and to be generally, but not always, associated with a rise in the total platelet count. Similar findings were recorded in human subjects on a diet high in animal fats, including milk fat and egg yolk. Thrombocytosis (usually obtained from egg yolk) reproduced these findings in the rabbit and in human patients with purpura.

Surgical and Accidental Trauma—As noted by Wright^{13d} and others,¹³⁹ platelet number and adhesiveness were generally observed to rise during convalescence from surgical operations or extensive trauma. In many instances, a slight rise in both factors appeared as early as one or two hours after operation, followed by a moderate fall which was perhaps indicative of increased utilization of platelets in the formation of wound thrombi. Beginning, as a rule, three to five days after operation, the total count and adhesiveness tended to rise progressively during a certain period and then fell gradually to normal. Similar findings were recorded after accidental trauma, especially fracture or severe contusion. Exceptions to this pattern of platelet behavior were not uncommon in this group, in certain instances, it was possible to demonstrate the presence of complications, particularly thrombosis.

Ischemic Necrosis (Myocardial Infarction, Peripheral Vascular Gangrene and Pulmonary Infarction)—These conditions were regularly accompanied, at least in their early stages, by a rise in platelet adhesiveness rivaling or surpassing that observed after operation. The total platelet count was often elevated as well, although not necessarily in corresponding degree. Later in the course of the acute stage, diminished counts, particularly of adhesive platelets, usually portended the formation of fresh thrombi of large size, e g, venous thrombi in the lower limbs or mural thrombi within the infarcted ventricle. The application of the platelet tests, particularly serial tests, was of much value in the diagnosis of recent myocardial infarction, especially before electrocardiographic confirmation, and as an indication for the administration of heparin sodium and dicumarol,[®] as described later in this paper.

¹³⁹ Starlinger and Sametnik²⁸ Lampert^{30f} von Seemen and Binswanger^{44e} Spooner and Meyer^{138b}

Cutaneous Irritation—As mentioned previously, extensive dermatitis, cutaneous irritation by chemical or physical agents or injections of bacterial or chemical irritants into the subcutaneous tissues have long been known to evoke a sharp rise in the platelet count¹⁴⁰ All patients with dermatitis and cellulitis studied by the glass wool filter test were observed to show, in addition, a considerable increase in platelet adhesiveness

Cancer—A number of cases of cancer of various organs were studied by this method In all, the adhesiveness of blood platelets was persistently high, although the total count was only moderately elevated or normal Complicating thrombosis was observed in several of these cases, unrelated to surgical intervention and involving not only the peripheral veins but, in 1 case, the cardiac valves and the auricular appendage as well, as indicated previously In our experience, the predisposition to thromboembolic disease in cancer appears to be more closely related to platelet adhesiveness than to total count This observation may warrant inclusion among the indications for prophylactic use of anti-coagulants, particularly after surgical procedures Aside from its probable prognostic value in evaluating the possibilities of thromboembolism in proved cases of carcinoma, the determination of persistently high platelet adhesiveness may prove helpful in the differential diagnosis of suspected cancer in the absence of pathognomonic signs and in the early detection of occult cancer A decisive correlation between high platelet adhesiveness and undiscovered cancer may be anticipated a priori in carcinoma of the pancreas, in which thrombotic incidents are notoriously common¹⁴¹ On theoretic grounds, thrombosis may be explained by the fact that the tumor cells continue to produce secretion which, having no means of egress to the intestine, exerts a digestive action on the gland itself, reflected in the presence of mucinous foci^{141b} By the same mechanism, local areas of lipolysis and fat necrosis¹⁴² may appear, resulting in the mobilization of thrombocytosin The circulation of pancreatic enzymes (particularly lipase) in the blood stream, which is observed to be increased in this disease,¹⁴³ may contribute considerably to

140 Footnote 82 Bunting⁸³

141 (a) Sproul, E E Carcinoma and Venous Thrombosis The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis, *Am J Cancer* **34** 566, 1938 (b) Kenney, W E The Association of Carcinoma in the Body and Tail of the Pancreas with Multiple Venous Thrombi, *Surgery* **14** 600, 1943

142 Titone, M Ueber ungewöhnlich ausgebreitete Fettgewebs- und Gewebeskrosen bei Pankreaskrebs, *Virchows Arch f path Anat* **297** 416, 1936

143 Comfort, M W, and Osterberg, A E The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, *Proc Staff Meet, Mayo Clin* **15** 429, 1940

the mobilization of thrombocytosin from adipose tissue and, in addition, exert a detergent action resulting in the development of endothelial wettability

Thrombocythemia—A few patients were encountered in whom persistently high platelet count and adhesiveness, together with the tendency to recurrent thrombus formation, could not be explained by any of the several factors just enumerated. In these instances, the hematologic findings signaled a primary affection of the bone marrow. Erythremia (polycythemia vera) was diagnosed in 1 patient presenting residua of cerebral and coronary thromboses, thrombotic gangrene of one foot eventually necessitated amputation of the leg. In this case, the highest erythrocyte count observed was only 6,470,000 per cubic millimeter, yet, the number of platelets rose to 1,224,000 per cubic millimeter, nearly all of which (1,126,000) were adhesive, and sternal aspiration revealed an exceptional number and segmentation activity of the megakaryocytes. Paradoxically, the patient suffered from repeated attacks of deep subcutaneous hemorrhage causing enormous painful hematomas. In another patient, gangrene of the leg followed thrombosis of the femoral artery complicated by a propagating thrombus of the accompanying vein. Although she presented no evidence of polycythemia at the time, the peripheral blood exhibited a striking leukemoid reaction in the course of secondary infection of the amputation stump, the leukocyte count reaching 95,000 per cubic millimeter, with a high proportion of myelocytes. The blood platelet count was excessive, rising to 702,000 cells per cubic millimeter, of which about 40 per cent were adhesive. At autopsy, nodular myeloid hyperplasia was demonstrated in the bone marrow, unassociated with evidences of leukemia, multiple benign tumors were present in the liver (cholangiomas), and a benign hypernephroid tumor was found in one kidney. In a third patient, a young woman of 31, neither erythroid nor myeloid overgrowth was present, the entire picture being that of "idiopathic thrombocythemia" (Rosenthal^{69g}) complicated by thrombosis of the splenic vein, which caused a succession of attacks of painful swelling of the spleen leading to its permanent marked enlargement. The platelet count initially was 580,000 per cubic millimeter, with a high proportion of adhesive platelets. After removal of the spleen, which was about ten times normal size (its weight was 1,100 Gm), the platelet count rose to 2,800,000, with a corresponding rise in the proportion of adhesive platelets. During several months' observation subsequently, little change was noted in the persistently high platelet number and platelet adhesiveness and the patient remained clinically free of thrombosis. Surprisingly, however, she manifested chronic gingival bleeding and occasional purpura of the skin. The bleeding time was somewhat prolonged and the capillaries of the nail fold, viewed microscopically, were widely

dilated and somewhat tortuous, recalling the findings considered characteristic of idiopathic thrombopenic purpura¹⁷ As in the patient with erythremia previously mentioned, the hemorrhagic tendency appeared to be independent of platelet count and adhesiveness, both of which were exceptionally high It is difficult to reconcile this apparent discrepancy except by speculation based on analogy If a comparison is made with certain benign tumors, the possibility may be suggested that these conditions, individually or in their collective form (erythroleukemia, as described by di Guglielmo^{133d}), represent the counterpart in the bone marrow of benign tumors of other tissues, being characterized by excessive proliferation of one or more hematic cell strains and by correspondingly defective functional worth and impaired capacity to respond to the normal controlling influences of the body, among which may be included the action of the splenic hormone The analogy is strengthened by the frequency with which erythremia or erythroleukemia terminates in true leukemia¹⁴⁴ At present, studies are being undertaken to test the hypothesis that the functional defect in the platelets responsible for bleeding in these cases¹⁴⁵ resides in their vasoconstrictor elements

Thrombosis and Embolism—Although thromboses which were recognized clinically or proved at autopsy developed in only a minority of patients in the preceding categories, sufficient data were accumulated to justify the following generalizations

1 A rising or persistently elevated count of adhesive platelets in the circulating blood is a consistent laboratory finding in the prodromal phases of thrombosis An elevation of the total platelet count is frequently, but not regularly, present

2 A rapid fall in the platelet count, comprising chiefly a drop in the number of adhesive platelets, often coincides with the formation of a white thrombus

Information is still lacking on the minimal size of a white thrombus required to produce an unmistakable change in the platelet picture Present data suggest that only thrombi forming in large veins and mural thrombi of the cardiac chambers affect the count significantly

The time between a drop in the platelet count and the earliest signs of manifest thrombosis is also indeterminate In general, signs of pulmonary embolism or infarction, reflecting the detachment of red thrombi from foci still clinically silent locally, first came to our notice three or more days after a fall in the platelet count had begun Several days more elapsed, as a rule, before local signs of phlebitis were recognized

144 Rosenthal^{69e} Rosenthal, N, and Bassen, F A Course of Polycythemia, Arch Int Med 62 1903 (Dec) 1938

145 Footnote 69 f, g and h Tinney, W S, and Giffin, H Z Hematologic Complications of Polycythemia Vera, Proc Staff Meet, Mayo Clin 18 227, 1943

A cyclic platelet curve was observed in patients with large propagating venous thrombi which gave rise to recurrent emboli and infarcts of the lung

On several occasions, a transient fall in both platelet count and platelet adhesiveness was encountered in predisposed patients without subsequent confirmatory signs or symptoms of thrombus formation. These instances were interpreted as probably the result of "silent thrombosis," comprising either nonobstructing mural platelet thrombi or occluding mixed thrombi of moderate size which resolve or undergo quiet organization and first come to light much later as the cause of superficial varicose veins. The frequency of such inapparent thromboses with or without undetected pulmonary embolism is now recognized as much higher than that of manifest thrombosis. Rossle^{58a} reported in 1937 an incidence, as observed at autopsy, of thrombi of the veins of the calf in 27.1 per cent of persons over 20. Neumann^{93f} (1938) reported venous thrombi in 100 of 165 consecutive autopsies, and Hunter and his associates^{44b} (1945) demonstrated deep venous thromboses in the legs of over 50 per cent of 400 adults at autopsy. On the other hand, clinically manifest thrombotic disease was reported by Barker and Priestley¹⁴⁶ to follow 0.96 per cent of all operations, about 2 per cent of laparotomies and 3 per cent of operations on the female pelvis. On the basis of the previous data, it may be estimated that only about 2 per cent of calf vein thrombi occurring in persons convalescing from operations actually become clinically demonstrable, either in situ or by reason of embolism.

Tests of blood coagulability often paralleled changes in platelet count and adhesiveness, but many discordant results were obtained. In several cases, comparative serial studies were made of prothrombin time (Quick), heparin tolerance (in vitro)^{100h} and clot retraction time^{97a}. From an analysis of time relationships, it seems likely that increased activity of clotting factors in the circulating blood can be explained in large part as the result of increased lysis of blood platelets (probably in the substance of developing white thrombi), resulting, in turn, in the accelerated conversion of prothrombin to thrombin at such sites. Increased clotting activity occasionally developed abruptly in the wake of a sharp rise in platelet count and adhesiveness. During the phase of thrombus development, mirrored in a fall in adhesive platelets, tests of clotting activity were often at variance but exhibited a downward trend in many instances, possibly as an indication of the withdrawal of clotting factors in the formation of large red thrombi.

146 Barker, N. W., and Priestley, J. T. A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. I. Incidence in Various Types of Operations, *Proc. Staff Meet., Mayo Clin.* **15**: 769, 1940.

Administration of Heparin Sodium and Dicumarol®—Coincidentally with the administration of heparin sodium in sufficient dosage to prolong coagulation time to a range of fifteen to thirty minutes or longer, the number of adhesive platelets dropped promptly from a high level to normal or below in each of the patients tested. In 1 case, ordinary doses of heparin sodium caused the apparent disappearance of all adhesive platelets. The total count tended to rise concurrently with a fall in adhesiveness. On the withdrawal of heparin sodium, the adhesive count returned to its previous level or higher and the total count dropped proportionately. The heparin-induced rise in the total count was interpreted as the prolonged survival of platelets in circulation due to reduced lysis, which was the result of the inhibited formation of thrombin, the normal activator of platelet adhesiveness and lysis.^{15b} The post-heparin rebound in the adhesive platelet count was accompanied in these patients with shortened prothrombin time, which was attributed to accelerated platelet lysis, and hence to increased liberation of the platelet accelerator^{36a, b} of prothrombin activation. A fall in total platelet count through heparinization has not yet been encountered in human beings, contrary to Copley's observations in dogs and hamsters (but not in mice)^{69d}

A moderate fall in platelet adhesiveness was observed in patients treated with dicumarol® in whom prothrombin activity had been maintained inadvertently for three days or longer at levels recorded as "less than 10 per cent." The platelet adhesiveness dropped in such cases into the lower range of normal but not below, in contrast to the striking drop below normal obtained with heparin sodium.

The prophylactic value of heparin sodium and dicumarol® has been established beyond dispute, and their use has contributed to a spectacular lowering of the incidence and mortality rate of thromboembolism following surgical intervention.¹⁴⁷ A similar program is apparently bearing fruit in the field of cardiology¹⁴⁸ and peripheral vascular disease.¹⁴⁹

147 Murray and others^{37h} Jorpes^{44a} Allen, Barker and Hines^{50a} Bauer^{93c} Allen^{121b} Barker, N W, Hines, E A, Jr, Kvale, W F, and Allen, E V. Dicumarol. Its Action, Clinical Use and Effectiveness as an Anticoagulant Drug, *Am J Med* **3** 634, 1947.

148 Wright and Foley^{50d} Nichol, E S, and Page, S W, Jr. Dicumarol Therapy in Acute Coronary Thrombosis. Results in Fifty Attacks, with Review of Data on Embolic Complications and Immediate Mortality in Myocardial Infarction, *Florida M A J* **32** 365, 1946. Peters, H R, Guyther, J R, and Brambel, C E. Dicumarol in Acute Coronary Thrombosis, *J A M A* **130** 398 (Feb 16) 1946.

149 Allen, Barker and Hines^{50a} Lange and Boyd⁵⁷ Brambel, C E, and Loker, F. Application of Dicoumarin (3,3'-Methylene-Bis-[4-Hydroxycoumarin]) in Trauma and Gangrene, *Arch Surg* **48** 1 (Jan) 1944. Lange, K, and Loewe, L. Subcutaneous Heparin in Pitkin Menstruum for Treatment of Experimental

The effect of anticoagulants is probably twofold (1) the retardation of clotting, restricting the formation and propagation of red thrombi, and (2) the reduction of platelet adhesiveness, restricting the formation of white thrombi. Both effects, in the last analysis, represent the suppressive action of these agents on the formation of thrombin, as previously indicated. Certain clinical and experimental data suggest, in addition, that these agents favor the resolution of red thrombi already formed.¹⁵⁰ According to von Kaulla,¹⁵¹ the role of plasma proteases having fibrinolytic activity deserves further study in relation to the spontaneous disappearance of thrombi. Morawitz¹⁵² apparently also anticipated the possibility that thrombi already formed may dissolve under the action of a specific fibrinolytic ferment, at least in the hemorrhagic tendency induced by phosphorus necrosis of the liver. Although Ferguson and Glazko¹⁵³ attributed antiproteolytic properties to heparin, Horwitt¹⁵⁴ indicated that that effect is relatively slight in the case of ordinary doses of heparin sodium and probably does not constitute part of its physiologic action. Accordingly, it may be postulated that heparin sodium not only inactivates and blocks the production of thrombin but leaves undisturbed the continued activity of fibrinolytic (and thrombinolytic?) enzymes previously liberated in the initiation of the clotting process, explaining thereby the apparent clot-dissolving property of heparin sodium in the case of red thrombi. From experimental observations, Loewe and others^{150b} concluded that dicumarol® also favors the resolution of thrombi, although much less effectively than heparin sodium.

Attempts to establish standards of dosage for heparin sodium and dicumarol® based on changes induced in platelet adhesiveness proved unsuccessful in our experience. No advantage was found in employing the fall of platelet adhesiveness as a criterion of effective dosage of

Human Frostbite, Surg, Gynec & Obst **82** 256, 1946. McLean, J., and Johnson, A. B. Gangrene Following Fracture Treated with Heparin, Papaverine and Intermittent Venous Occlusion. Report of Case, Reasons for Using Heparin, Surgery **20** 324, 1946. Allen, E. V. The Emergency Treatment of Vascular Occlusions, J. A. M. A. **135** 15 (Sept 6) 1947.

150 (a) Rabinovitch, J., and Pines, B. Effect of Heparin on Experimentally Produced Venous Thrombosis, Surgery **14** 669, 1943. (b) Loewe, L., Hirsch, E.; Grayzel, D. M., and Kashdan, F. Experimental Study of the Comparative Action of Heparin and Dicumarol on the in Vivo Clot, J. Lab & Clin Med **33** 721, 1948.

151 von Kaulla, K. N. Betrachtungen zur postnarkotischen Fibrinolyse, Schweiz med Wchnschr **77** 313, 1947.

152 Morawitz, cited by Frank⁶⁹¹.

153 Ferguson, J. H., and Glazko, A. J. Heparin and Natural Antiprothrombin in Relation to Activation and "Assay" of Prothrombin, Am J Physiol **134** 47, 1941.

154 Horwitt, M. K. Trypsin and Chymotrypsin Versus Heparin, Science **101** 376, 1945.

heparin sodium over the use of standard methods for measuring coagulation time. On the other hand, abnormal bleeding following the administration of either heparin sodium or dicumarol® appeared in certain cases in which the dosage was insufficient to reduce platelet adhesiveness below normal. On the withdrawal of anticoagulants, the prolongation of bleeding time occasionally persisted long after the coagulation time, prothrombin time and platelet adhesiveness had returned to their previous level.

The occurrence of a bleeding tendency in the presence of normal coagulation time, normal prothrombin time and normal or elevated platelet adhesiveness, as in the instances mentioned, introduces the possibility that the underlying fault lies within the blood vessels. Heparin sodium given to mice was reported by Copley and Lalich¹⁵⁵ to cause prolonged bleeding time when given in excessive doses, the result was attributed to the exhaustion of an unidentified factor in the tissues. The experiments of Rigdon and Wilson¹⁵⁶ suggest that heparin sodium has no effect on capillary permeability as such or on the development of inflammation. Generalized vasodilatation has been produced experimentally by overdosage with dicumarol® (Bingham¹⁵⁷, Dale and Jaques^{10d}). Suggestive data have also been obtained with hirudin. Jurgens cited Roskam's experiments and his own^{9j} to show a direct action of hirudin on endothelium which parallels or exceeds its effect on platelets, being prolonged beyond the duration of the latter and preventing platelet agglutination and the attachment of clot to traumatized endothelium and contiguous wound surfaces.

An alternative possibility which may deserve further study involves the concept of the blood platelet as a "solid secretion" which undergoes physiologic breakdown to liberate a vasoconstrictor substance in support of normal vascular contractility and tonus, as mentioned previously. It remains to be shown whether or not heparin and other anticoagulants effective *in vivo* exert their effect on blood vessels indirectly, perhaps by impairing the biologic effectiveness of blood platelets as a source of a vasoconstrictor substance. It is conceivable that if such an effect can be demonstrated it may occur selectively, without the impairment of adhesiveness or other known properties of platelets. The possibility that such dissociation in platelet properties may exist is suggested by the described findings in erythremia and idiopathic thrombocythemia.

155 Copley, A. L., and Lalich, J. J. The Experimental Production of a Hemophilia-like Condition in Heparinized Mice, *Am J Physiol* **135** 547, 1942.

156 Rigdon, R. H., and Wilson, H. Capillary Permeability and Inflammation in Rabbits Given Heparin, *Arch Surg* **43** 64 (July) 1941.

157 Bingham, J. B., Meyer, O. O., and Pohle, F. J. Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, *Am J M Sc* **202** 563, 1941.

POSSIBLE ROLE OF SPLEEN IN PREVENTION OF FORMATION
OF WHITE THROMBUS

The premise that the spleen normally plays a part in protecting the circulation against intravascular thrombi is supported by a variety of evidence. Surgical removal of the spleen is followed by a greater incidence of distant thrombosis than any other operation of equivalent magnitude¹⁵⁸. Although a pronounced rise in the platelet count occurs after splenectomy, the determining factor in thrombosis is more likely the qualitative alterations in platelets (referred to previously), manifested as increased agglutinability and adhesiveness. Rosenthal, who was one of the first to suggest that the role of the spleen in purpura was bound up with its power to alter the quality of the blood platelets,^{69f} also posulated an active role of the spleen in suppressing thrombus formation in patients with an excessively high platelet count (idiopathic thrombocythemia¹⁵⁹). Removal of the spleen in cases of thrombopenic purpura has been shown repeatedly to result in permanent cure of the bleeding tendency even when the platelet count returns to its former low level,¹⁶⁰ adding further weight to Rosenthal's concept that the spleen is concerned with the quality of the platelets. It is reasonable, therefore, to postulate that deficient function of the spleen may be one of the predisposing factors in thromboembolism and that excessive function of the spleen ("hypersplenism") may suppress the formation of thrombi by its effect on platelet qualities, even to the point of inducing a hemorrhagic tendency. This is an extension of the old theory of a suppressive splenic hormone¹⁶¹.

Our studies of platelet adhesiveness in thrombopenic purpura appear to lend support to the general concept of hypersplenism. In the "idiopathic" type, presumably caused by hyperfunction of the spleen, platelet adhesiveness was found to be extremely low or virtually absent. A similar state was encountered in a case of splenomegaly complicating coarse nodular cirrhosis. In "secondary" thrombopenic purpura resulting from leukemic infiltration of the bone marrow (and spleen), platelet adhesiveness was undiminished or relatively increased, despite the marked lowering of the total platelet count. These data suggest that

158 Allen, Barker and Hines^{50a} Barker and Priestly¹⁴⁶

159 Rosenthal^{69e} Rosenthal^{125d}

160 Jurgens^{11d} Jurgens and Graupner^{66f} Brill and Rosenthal^{69d} Rosenthal^{69e}
Footnote 71 *c* and *d*

161 (a) Frank^{12e} (b) Frank⁶⁹ⁱ (c) Footnote 86 *c*, *d* and *e* (d) Isaac (1912), Turk, Naegeli, Bock and Franzel, Jombres, Buchem, cited by Hirschboeck, J. S. Hematologic Effects of Splenectomy in Still-Chauffard-Felty Syndrome. A Report of Two Cases, *Blood* 1:247, 1946 (e) Engelbreth-Holm, J. A Study of Tuberculous Splenomegaly and Splenogenic Controlling of the Cell Emission from the Bone Marrow, *Am J M Sc* 195:32, 1938

two separate mechanisms underlie most instances of thrombopenia (1) hormonal suppression of megakaryocytic segmentation and (2) quantitative reduction in the number of megakaryocytes. The former results in both qualitative and quantitative changes in blood platelets, the latter, in quantitative changes alone. This difference in mechanism may account for the greater tendency to hemorrhage in hypersplenic purpura than in secondary purpuras having a similar numerical platelet count^{18f}

The presence of thrombopenia and hemorrhagic tendency in certain systemic infections as well as in "idiopathic" thrombopenic purpura suggests a common background of hyperplasia of the elements in the spleen which are comprised in the reticuloendothelial system. In general, such infections may be classified as proliferative reticuloendothelioses, characterized in their florid stages by anergy rather than allergy, and by systematization rather than localization or encapsulation¹⁶². In this group may be included infectious mononucleosis,¹⁶³ brucellosis,^{163c} typhoid,^{69h} abdominal lymphogranulomatosis,¹⁶⁴ malaria,^{69h} sarcoidosis,¹⁶⁵ miliary tuberculosis,¹⁶⁶ kala-azar,¹⁶⁷ Felty's syndrome¹⁶⁸ and long-standing *Streptococcus viridans* endocarditis¹⁶⁹. In most instances, thrombopenia is moderate, purpura is an infrequent complication but may be severe. Leukopenia is also common, yet, extreme granulocytopenia is rare except, perhaps, in kala-azar¹⁶⁷. In infectious mono-

162 Moolten, S. E. Characterization of Systemic Infection Which Is Principally Proliferative (The Pattern of Infectious Reticulo-Endotheliosis), Lecture XV, An Interpretive Course in Pathology for the Clinician, New Brunswick, N. J., Rutgers University, 1947. Mimeographed copies available from the author.

163 (a) Rosenthal^{71c} (b) Magner, W., and Brooks, E. F. Infection Mononucleosis with Acute Thrombopenic Purpura, *Bull. Acad. Med. Toronto* **15** 189, 1942 (c) Damashek, W., and Grassi, M. A. Infectious Lymphadenosis ("Mononucleosis") and Thrombocytopenic Purpura. Recovery After Splenectomy, *Blood* **1** 339, 1946.

164 Frank⁶⁹ⁱ Schousboe^{86d}

165 Isaac and others^{161d} Personal observation. Posner, I. Sarcoidosis. Case Report, *J. Pediatrics* **20** 486, 1942.

166 Rosenthal^{71c} Engelbreth-Holm^{161e} Kellert, E. Miliary Tuberculosis of the Spleen with Thrombopenic Purpura Hemorrhagica, *J. A. M. A.* **96** 2193 (June 27) 1931.

167 Frank⁶⁹ⁱ Cartwright, G. E., Chung, H. L., and Chang, A. Studies on the Pancytopenia of Kala-Azar, *Blood* **3** 249, 1948.

168 Personal observation. Hirschboeck, J. S. Hematologic Effects of Splenectomy in Still-Chauffard-Felty Syndrome. A Report of Two Cases, *Blood* **1** 247, 1946.

169 (a) Rosenthal, N. The Blood Picture in Purpura, *J. Lab. & Clin. Med.* **13** 303, 1928 (b) Jaffe, R. H. Bone Marrow in Agranulocytosis (Pernicious Leukopenia), *Arch. Path.* **16** 611 (Nov.) 1933.

nucleosis, recently observed in a boy of 7 years, the platelet count dropped to 66,000. Two days later it rose again to 146,000, but adhesive platelets remained scarce (24,000), bleeding time was somewhat prolonged, and capillary fragility was increased. Transient leukopenia (the count was 1,860) was also present. A reduction in platelet adhesiveness without thrombopenia was also noted in a female patient with chronic brucellosis. Contrary to the general rule, she exhibited virtually no elevation of either platelet count or platelet adhesiveness following an extensive surgical procedure, this may have been another indication of hypersplenism.

Splenic enlargement accompanied with lymphoid hyperplasia, which is characteristic of exophthalmic goiter,¹⁷⁰ possibly explains the tendency to thrombopenia and the excessive tendency to hemorrhage¹⁷¹ which may prove troublesome during or immediately after thyroidectomy.^{171b} Outspoken purpura, however, is rare.^{134f} Similar tendencies have been recorded in women during phases of increased estrogenic activity¹⁷² and, in extreme form, probably account for menstrual purpura^{172b, d} and menstrual exacerbations of purpura, as well as for purpura occurring during the latter months of pregnancy.¹⁷³ These and other endocrine interrelationships with splenic function may be mediated or controlled through the hypophysis.¹⁷⁴ A distinct lowering of platelet adhesiveness was found by us to characterize both hyperthyroidism and pregnancy at term, although in the cases studied the total platelet count was normal or even slightly increased. Platelet tests in a few parturient women showed some variation in the rate of rise of platelet count and

170 Lauda^{86c} Benson, Ott and Scott, Hewitt, Cameron and others, cited by Lauda^{86c}

171 (a) Woodruff^{134f} (b) Bechgaard, P. Tendency to Hemorrhage in Thyrotoxicosis, *Acta med Scandinav* **124** 79, 1946

172 (a) Lee and Erickson^{67b} (b) Minot, G. R. Purpura Hemorrhagica with Lymphocytosis. An Acute Type and an Intermittent Menstrual Type, *Am J M Sc* **192** 445, 1936 (c) Pohle, F. J. The Blood Platelet Count in Relation to the Menstrual Cycle in Normal Women, *ibid* **197** 40, 1939 (d) Goldburgh, H. L., and Gouley, B. A. Postpubertal Menorrhagia and Its Possible Relations to Thrombocytopenic Purpura Hemorrhagica, *ibid* **200** 499, 1940

173 Leschke and Wittkower^{71d} Rosenthal^{168a} Troland and Lee,⁸⁷ case 1 Burnett, G. W. F., and Klass, I. A Review of the Problem of Purpura During Pregnancy, *J Obst & Gynaec Brit Emp* **50** 393, 1943 Finn, W. F. Thrombocytopenic Purpura in Pregnancy. Review of Literature with Report of Three Cases, *Am J Obst & Gynec* **48** 497, 1944

174 Perla, D. Relation of the Hypophysis to the Spleen. I Effect of Hypophysectomy on Growth and Regeneration of Spleen Tissue, II The Presence of a Spleen-Stimulating Factor in Extracts of Anterior Hypophysis, *J Exper Med* **63** 599, 1936

adhesiveness after delivery, but in none was thrombosis diagnosed. Two parturient women exhibited many giant platelets in blood smears taken during the early puerperium.

Action of Thrombocytopen—The belief that the spleen exerts its physiologic control over platelet number and quality through the agency of a specific hormone, thrombocytopen, has gained increasing acceptance in recent years¹⁷⁵ with the continued accumulation of authoritative data confirming the findings of Troland and Lee⁸⁷ (1938). In all published studies, the sole concern has apparently been the effect of relatively crude aqueous extracts containing thrombocytopen on the total platelet count of rabbits and other animals. When one of us (S. E. M.) was also occupied with the problem of the isolation of thrombocytopen from the spleen of purpura hemorrhagica⁷⁵ (1944-1945), his attention was likewise directed to the action of thrombocytopen in reducing the platelet count. As an outcome of that study, it was determined that thrombocytopen was of lipid nature and was a product of the normal spleen. The problem of its separation from other splenic lipids was simplified greatly when the existence of its specific biologic antagonist, thrombocytosin, was demonstrated and measures were devised to separate the latter (also a lipid) from the mixture. As mentioned, thrombocytosin is also abundant in adipose tissue, lymph nodes and egg yolk. At that time and subsequently, procedures were developed which made it possible to obtain these substances in a more or less refined state and in suitable amounts for experimental and clinical use. Among the results of these later studies has been the discovery, mentioned previously, that thrombocytopen (usually obtained from bovine spleen) and thrombocytosin (usually obtained from egg yolk) exert their mutually antagonistic influence not only on platelet number but on platelet adhesiveness as well. The effect on adhesiveness was measured by the glass filter method in samples of human or rabbit blood after the oral or parenteral administration of these substances to the living subject or after their addition in high dilution (0.001 per cent) to the citrated specimen of blood in vitro. In rabbits, 5 mg. injections of either substance were regularly effective in producing its specific response. In human patients, significant effects were obtained with doses of 25 to 50 mg., given intramuscularly in aqueous suspension or dissolved in oil. Single doses of 100 mg. of thrombocytopen in human subjects were consistently effective in lowering total platelet count and platelet adhesiveness from high levels to normal levels or slightly below for two to four days, the lowering was generally attended with a slight initial prolongation of

¹⁷⁵ Major and Weber (1939), Hobson and Witts (1940), Rose and Boyer (1941), Otenasek and Lee (1941), Paul (1942), Uihlen (1942), Cronkite (1944), cited by Moolten⁷⁵. Dameshek and Dekanes, cited by Dameshek and Miller²²

bleeding time Comparable doses of thrombocytosin in cases of purpura had the opposite effect, raising platelet adhesiveness and, to some extent, total platelet count, and shortening bleeding time, as described

CONCLUSIONS

The data given in the body of this paper, including the experiences just cited, are believed to justify the following hypotheses regarding the role of the spleen in thrombosis and in hemostasis

- 1 By the agency of thrombocytopen, a lipid hormone produced in its reticuloendothelial elements, the spleen normally exerts a moderating influence on the tendency to thrombus formation

- 2 This effect depends on the capacity of thrombocytopen to limit the number and adhesive quality of blood platelets and, thereby, to retard the formation and growth of white thrombi

- 3 An increased number and adhesiveness of blood platelets and, hence, an increased predisposition to the formation of massive thrombi, result from the action of thrombocytosin, a lipid substance normally present in subcutaneous fat and mobilized therefrom by trauma or lipolytic ferments or absorbed into the circulation as a dietary factor occurring in fatty materials of animal origin

- 4 The relatively stable range of the total platelet count and, particularly, of the adhesive platelet count under normal conditions is evidence of an adaptative mechanism which constantly adjusts the functional activity of the spleen in order to protect the organism against the effects of widely fluctuating amounts of thrombocytosin entering the circulation

It remains a hopeful objective for the future to determine whether or not thrombocytopen can be utilized practicably in the human being for reducing excessive platelet adhesiveness in the prophylaxis of thromboembolism

SUMMARY

The massing of blood platelets as an adherent plug is the primary event in thrombosis, as it is in the arrest of hemorrhage Clotting is its sequel and rapidly follows lysis of the accumulated platelets, wherein clot-accelerating factors are liberated The platelet plug (white thrombus) is the principal means of attachment of the blood clot (red thrombus) until the latter is organized by invading fibroblasts Clot retraction before organization favors the detachment of emboli

Endothelial "wettability" and platelet adhesiveness are the principal governing factors in thrombosis Experiments are described demonstrating relative nonwettability in unopened blood vessels and the progressive development of wettability under conditions which probably favor thrombosis Analogous conditions probably also exist in arteries damaged by atheroma, prolonged spasm or compression, in veins sub-

jected to angulation, compression or inflammation, and on the intravenous introduction of fat solvents such as ether and alcohol or of detergent agents, including the saponins of crude digitalis. Endocardial vegetations and mural thrombi in the heart may be similarly caused.

An increase in the number and adhesiveness of platelets results from the action of thrombocytosin, a lipid of body fat, which is probably liberated by direct trauma (e g, surgical incisions, fractures, cutaneous irritations or cellulitis), by proteolytic or lipolytic ferments activated by tissue breakdown of any type (e g, myocardial infarction, vascular gangrene or carcinoma) or after the ingestion of dietary fat of animal origin. Thrombocytopen, a lipid of the spleen which suppresses platelet formation and adhesiveness, is probably the physiologic antagonist of thrombocytosin.

A new method of measuring platelet adhesiveness to wettable surfaces is described in which citrated blood is filtered through a wick of glass wool, the relative loss of platelets by adsorption is computed as the "adhesive index," from which the proportion of adhesive platelets is calculated. A marked increase in platelet adhesiveness suggests a predisposition to thrombosis, whereas a pronounced decrease in adhesiveness is found in purpura associated with splenic hyperfunction. Platelet adhesiveness is particularly high and persistent in cancer, paralleling an increased tendency to thrombosis. Similar findings occur in polycythemia vera, idiopathic thrombocythemia and related conditions, which probably represent primary disorders of the bone marrow rather than a response to thrombocytosin.

A rapid fall in the platelet count, and particularly in the number of adhesive platelets, from a previously high level often portends the formation of thrombi and aids in their preclinical recognition. Increased coagulability of the blood is probably secondary to the accelerated production of thrombin about white thrombi. Heparin sodium tends to lower platelet adhesiveness and probably retards lysis. Dicumarol® has much less effect. Thrombocytopen causes a fall in the platelet count and adhesiveness and some prolongation of bleeding time, these effects suggest its practical value in the prophylaxis of thrombosis. Thrombocytosin, its antagonist, has been found useful in the therapy of purpura.

Deficient splenic function may be one of the factors which predispose to thrombosis. Conversely, normal splenic function may include protection of the circulatory tree against thrombosis.

CONCEPTS OF MYOCARDIAL ISCHEMIA

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MYOCARDIAL ischemia occurs whenever there exists a discrepancy between the available oxygen supply and the work requirements of the heart muscle. The balance of these two factors is essential for cardiac function. An arterial blood flow below that customarily available for work performance results in myocardial ischemia.

As shown in table 1, a decrease in oxygen supply to the heart muscle may be absolute, owing to narrowing of arterial caliber by occlusive disease, prolonged spasm or a decrease in the oxygen-carrying capacity of the blood (anemia). The decrease may be relative when the arterial supply provided for the normal heart must serve a greater muscular mass than normal (as in cardiac hypertrophy) or when the energy requirements exceed the maximal capacity of the coronary bed. It is also possible that the utilization of available oxygen is impaired either because oxygen is offered to the tissues in nonutilizable form (as in carbon monoxide poisoning) or because certain oxidation systems of the heart muscle cells are paralyzed (as in cyanide poisoning). The failure of oxygen utilization may be responsible for changes in the electrocardiogram observed during these states. It is rarely severe enough to be of clinical significance because irreparable respiratory paralysis occurs before the heart is permanently impaired.

The work of the heart, the second factor in table 1, is customarily divided into useful or external work, visibly expended in the propulsion of blood against peripheral resistance, and internal work, which may be expressed by the total energy liberated minus the external work performed. The ratio of energy liberated to work performed determines the efficiency of the heart muscle. The external work of the heart may be roughly estimated from cardiac output and peripheral resistance. As shown in figure 1, an increase in the work load is invariably associated with an increase in the coronary flow. The injection of large amounts of

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epinephrine into an experimental animal regularly increases the work requirements beyond the capacity of the coronary circulation, and severe myocardial ischemia results. The administration of epinephrine has been proposed as one of the tests for the efficiency of the coronary circulation in man, in whom a similar reaction, though a less severe one, may be induced. It is doubtful, however, that in subjects with an adequate blood supply to the heart muscle and in the absence of external stimulation with epinephrine the cardiac work load can be increased out of proportion to the available reserves of the coronary bed, although this inference has been made from time to time. On the other hand, a comparatively slight decrease in oxygen supply or oxygen utilization, which may be induced by a variety of etiologic factors, may be enough to induce myocardial ischemia in an apparently normal heart when cardiac work is increased due to any of the factors mentioned in table 1. Furthermore,

TABLE 1—*Causes of Myocardial Ischemia*

Cause	Condition
Decrease in oxygen supply	
Absolute	Disease of the coronary arteries, anemia
Relative	Cardiac hypertrophy, excessive external and internal work
"Chemical" (enzymatic?)	Failure of utilization
Increase in work requirement	
Due to increased heart rate	
Due to increased input and output load	Increased volume flow and increased peripheral resistance
Due to decreased efficiency	Structural defects, "chemical" factors

the heart is not an efficient organ. Only about 10 per cent of the available energy is expended as external work.¹ Without apparent changes in the work load of the heart, myocardial ischemia may develop if the efficiency decreases as the result of valvular defects or of poorly understood chemical (enzymatic?) processes preceding the onset of congestive heart failure. In this case, for a given task a greater than normal effort is needed, and the signs of ischemia may appear though the apparent work load is unaltered or actually decreased and the oxygen supply unchanged.

In figure 1, the physiologic imbalance responsible for the signs and symptoms of myocardial ischemia is indicated. As soon as a "point of tolerance" is reached, the limits of the available reserves are exceeded and myocardial ischemia ensues. When the blood supply to the working organ decreases below this point, a state of "coronary insufficiency" results. The term "myocardial ischemia" is preferred because it defines

1 Landowne, M, and Katz, L. N. Heart Work and Failure, in Glasser, O. Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, p. 578. (Includes further references.)

more clearly the functional alterations that take place. It is, of course, admitted that diseases of the coronary arteries constitute by far the commonest cause of myocardial ischemia. The syndrome occurs, however, without obvious anatomic alteration of the arteries themselves. It is not infrequently seen in the wake of severe infections, including diphtheria, or as the result of sensitivity reactions (serum sickness, rheumatic fever, streptococcic states). The mechanism by which oxygen supply and oxygen utilization are involved in such processes has not been elucidated in all instances. Indeed, an almost infinite variety of abnormal states and combinations of reactions may lead to the syndrome. Certain anatomic aspects of it have been discussed from time to time. The subendocardial location of the anatomic manifestations has usually been stressed.² As will be shown, there is strong electrocardiographic evidence that these may not be the only regions involved.

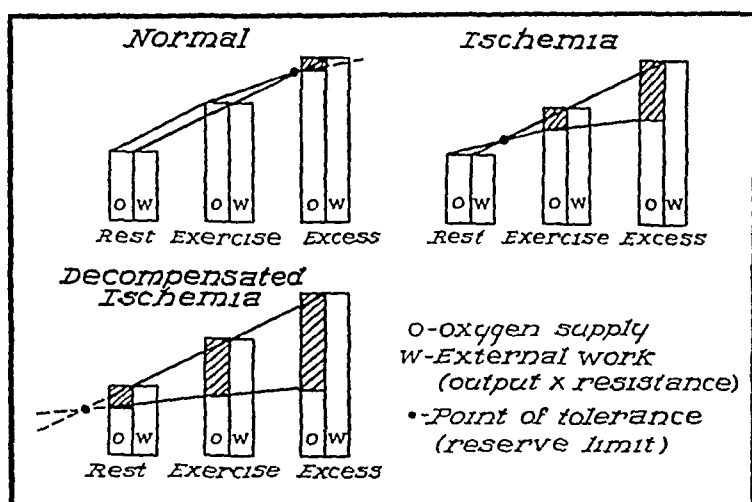


Fig 1—Discrepancy between oxygen supply and external work performance. An increase in internal work performed (change in metabolic requirements) may cause ischemia though external effort remains unaltered. Note that in progressive ischemia the point of tolerance is shifted to the left of the diagram.

It is obvious from the diagram that the determination of the point of tolerance—the limit of the available reserves—is of importance in the evaluation of the patient's condition. It is equally apparent that this determination requires that the patient be examined while subjected to increasing work loads (exercise), as signs and symptoms of the syndrome appear at rest only in decompensated severe myocardial ischemia.

2 (a) Buchner, F. Die Koronarinsuffizienz, Dresden, Steinkopff, 1939. (b) Master, A. M., Dack, S., Gishman, A., Field, L. E., and Horn, H. Acute Coronary Insufficiency. An Entity, J Mount Sinai Hosp 14:8, 1947. (c) Master, A. M. Acute Coronary Diseases, Am J Med 2:501, 1947. (Includes further references.)

CLINICAL AND ELECTROCARDIOGRAPHIC SIGNS

The clinical signs of this state should not be confused with those denoting diseases of the coronary arteries, although, of course, a good deal of overlapping exists. Table 2 indicates that the disorder under discussion is only one of the many manifestations of disease of the coronary arteries. It is admitted that ischemia may be the exciting factor in all, but conduction defects, cardiac irregularities and congestive heart failure obviously are of no value in gaging the presence or the intensity of the syndrome as they may appear from a variety of other causes.

Myocardial ischemia gives rise to two cardinal manifestations regardless of whether an anatomic lesion can or cannot be demonstrated—pain, and changes in the electrocardiogram (table 3).

TABLE 2—*Clinical Manifestations of Disease of the Coronary Arteries*

None
Conduction defects
Cardiac irregularities
Congestive heart failure
Myocardial ischemia

TABLE 3—*Clinical Manifestations of Myocardial Ischemia*

When few, if any, detectable anatomic lesions are present
Precordial pain
Electrocardiographic changes
When tissue destruction and repair are present
Precordial pain
Electrocardiographic changes
Physical findings
(Remote reactions [abnormal responses to laboratory tests] may occur)

Pain—This symptom constitutes the most important guide to the syndrome, but myocardial ischemia may be present without pain, and pain may arise from the myocardium in the absence of ischemia. Moreover, any visceral pain may be changed in intensity and character during its passage over afferent nerve fibers and is profoundly modulated at subcortical and cortical levels. If precordial pain is present it may signal myocardial ischemia, but it is of little value in the evaluation of the severity of the syndrome. Severe ischemia may be induced rapidly without the occurrence of pain. This is indicated by the observation that in 162 anoxia tests performed on 97 patients with myocardial ischemia, pain did not occur in 84 instances, or 50 per cent (table 6).

Electrocardiographic Changes—The second sign (table 3) appears far more reliable. A change in the pattern of the electrocardiogram may be taken as a sensitive and objective indicator. The value of the electro-

cardiographic examination may be enhanced if a complete selective exploration of various sections of cardiac muscle is carried out by a number of precordial, esophageal and unipolar limb leads. In the series mentioned, 90 per cent of the positive responses were associated with demonstrable electrocardiographic changes. Unless injury to tissue is excessive and has resulted in gross myocardial necrosis the alterations involve only the final portions of the ventricular electrocardiogram, namely, the RS-T segment and the T wave. These depend on (a) the degree of ischemia, (b) the location of the ischemic region and (c) the preexisting nutritional state of the myocardium. Figure 2 reveals that electrocardiograms obtained from a region subjected to mild ischemia are characterized by inversion of the terminal portion of the T wave or by accentuation of a previously inverted T wave (stage 1), and those indicating severer grades (injury), by elevation of the RS-T segment (stage 2). If the surface of the heart is damaged or if ischemia involves primarily the subepicardial region the electrocardiographic changes will be transmitted directly to the precordium and to other regions to which the effects of electrical excitation of epicardial layers are being transmitted, particularly to the left arm and to the left leg. If endocardial regions primarily are involved, changes in the RS-T segment and the T wave will be transmitted unchanged only to the right arm or to an electrode placed high in the esophagus. However, endocardial ischemia exerts a remote effect on the variations in electrical potential recorded by a precordial electrode or an electrode placed over the left arm or the left leg. These changes will be less intense than, and opposite in sign to, those recorded by an electrode placed in the vicinity of the endocardium. Consequently, in chest leads, and to a certain extent in standard leads, subepicardial ischemia is signaled by inversion of the T wave and elevation of the RS-T segment and an endocardial lesion by an upright T wave and by depression of the RS-T segment. Figure 2 illustrates the various combinations that may be encountered when one region is more intensely involved than the other.

The electrocardiogram of an ischemic region changes because the rate at which the area returns to the resting stage is prolonged (repolarization delay—stage 1 in figure 2). In the severer stages, the heart muscle of this region is electrically never completely at rest (flow of resting currents—stage 2 in figure 2). Uniform ischemia of all muscle layers or ischemia localized to regions deeply embedded in, and surrounded by, well functioning muscle will result in few, if any, electrocardiographic changes, it constitutes the ultimate limitation in electrocardiographic examinations. These considerations may explain the reported instances of myocardial infarction with apparently normal

electrocardiograms,³ although almost all instances on record lack a complete electrocardiographic work-up

The intensity of the abnormal reaction and the location of the area that is primarily involved mold the T wave of the electrocardiogram. This concept has found confirmation in many experimental animals and in human subjects exposed to various experimental procedures, and it may be substantiated on clinical grounds. It is possible, therefore,

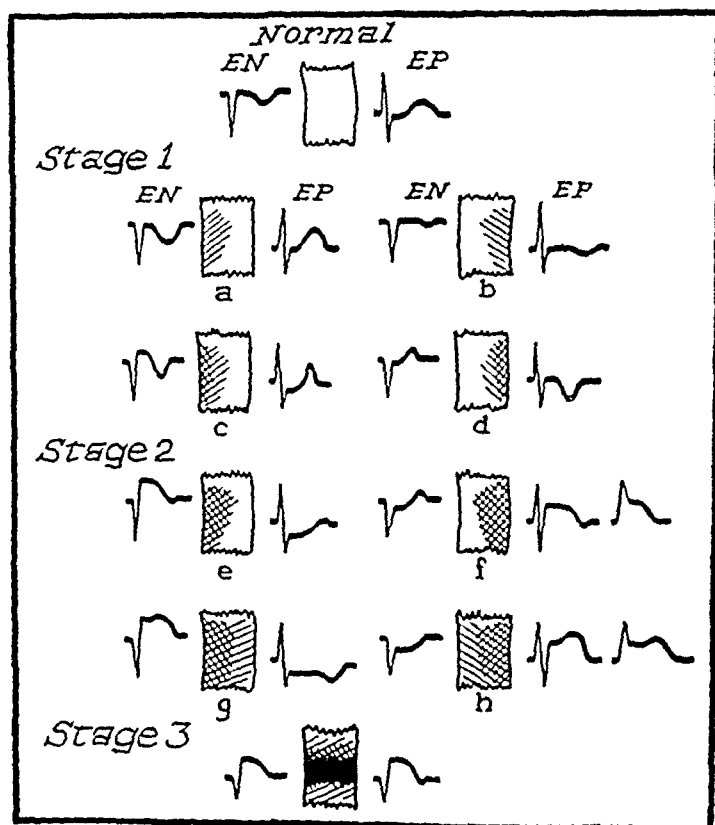


Fig 2—Changes in the RS-T segment and T wave in myocardial ischemia. A section of the heart muscle is shown with the endocardial surface (EN V_R , VE_{30-40}) facing to the left and the epicardial surface (EP V_1-V_6 , V_L , V_F , VE_{15-20}) to the right. Predominantly subendocardial ischemia is illustrated in the left column and predominantly subepicardial ischemia in the right column, the intensity of the process is indicated by hatching and cross hatching. Note that the epicardial electrocardiogram of endocardial injury (c), generally described as the pattern of "coronary insufficiency," presents only one of the many possibilities, g (subendocardial injury with subepicardial ischemia) yields a pattern that may simulate ventricular enlargement ("strain"). Stage 1 represents myocardial "ischemia" of Bayley (repolarization delay), stage 2 myocardial "injury" of Bayley (incomplete repolarization) and stage 3 myocardial ischemia with obvious destruction of tissue (infarction).

3 Langendorf, R, and Kovitz, B. Acute Myocardial Infarction Without Deviation of the ST Segment in the Electrocardiogram, *Am J M Sc* 204 239, 1942. Pirani, C L, and Schlichter, J G. Subendocardial Myocardial Infarct, *Ann Int Med* 25 847, 1946.

to expand the interpretation of figure 2 into an attempt to explain changes in the T wave in general

This approach implies that many types of changes in the T wave may result from myocardial ischemia. "Coronary insufficiency" has usually been described as resulting in flattening of the T wave and in depression of the RS-T segment². Such a statement is incomplete, as it describes only the epicardial pattern of severe endocardial ischemia (fig 2, stage 2, muscle strip on the left). It is also true, however, that this pattern is frequently seen in conditions associated with myocardial ischemia. One must conclude that the endocardial surfaces are more vulnerable than other sections of cardiac muscle, a well known fact that has recently been confirmed again by experiments with the infusion of fluorescein sodium⁴.

Induced anoxemia or spontaneously occurring myocardial ischemia may reveal any of the types of changes in the S-T segment and the T wave in figure 2⁵. Terminal inversion of the T wave without displacement of the R-T segment, apparently signalling predominant subepicardial ischemia, may occur in cases of hypertrophy of the left ventricle. Typical examples of this kind of change in the T wave are indicated in figures 3 and 4 and should be contrasted with the pattern of "coronary insufficiency" of Master and others^{2b,c}.

Long-standing severe ischemia or sudden temporary cessation of the blood supply to one area may lead to necrosis of muscular tissue, which is best seen in true myocardial infarction secondary to occlusion of a coronary artery. When such destruction of tissue occurs, a number of new signs appear. The electrocardiogram reveals, in addition to the changes of ischemia, a sharp reduction in the R wave of the QRS complex with the appearance of the Q waves in regions dominated by epicardial effects. An epicardial lead then resembles a lead taken from the cavities (stage 3, fig 2), because the endocardium and the epicardium are separated by a layer of nonfunctioning (necrotic) tissue which does not become involved in the process of activation. The complex electrocardiographic picture of myocardial infarction with (a) an excessively deep Q wave, (b) elevation of the RS-T segment and (c) changes in the terminal portion of the T wave resolves itself readily into evidence of necrosis and scarring, severe injury and milder states of ischemia (fig 5). These patterns may be recorded in succession when in

4 Prinzmetal, M., Bergman, H. C., Kruger, H. E., Schwartz, L. L., Simkin, B., and Sobin, S. S. Studies on the Coronary Circulation. III Collateral Circulation of Beating Human and Dog Hearts with Coronary Occlusion, *Am Heart J* 35 689, 1948

5 Hecht, H. H., Abildskov, J., Bolin, R., and Focht, F. S. Observations on the Human Heart During Induced Hypoxia (the Ischemia-Injury Pattern), *Am J Med* 4 623, 1948

experimentally induced infarction an electrode is moved from the center of the infarct toward the periphery⁶ They may be seen in patients examined by serial precordial leads, and in whom the inversion of the T wave (a sign of mild ischemia surrounding the infarcted region) is usually observed over a larger area than is elevation of the RS-T segment and the Q wave They explain the succession of electrocardiographic changes over a period of time in patients recovering from such an episode Figure 6 illustrates the changes that occur in time and space in patients with myocardial infarction With the exception of Q waves which usually though not always indicate transmural necrosis, the

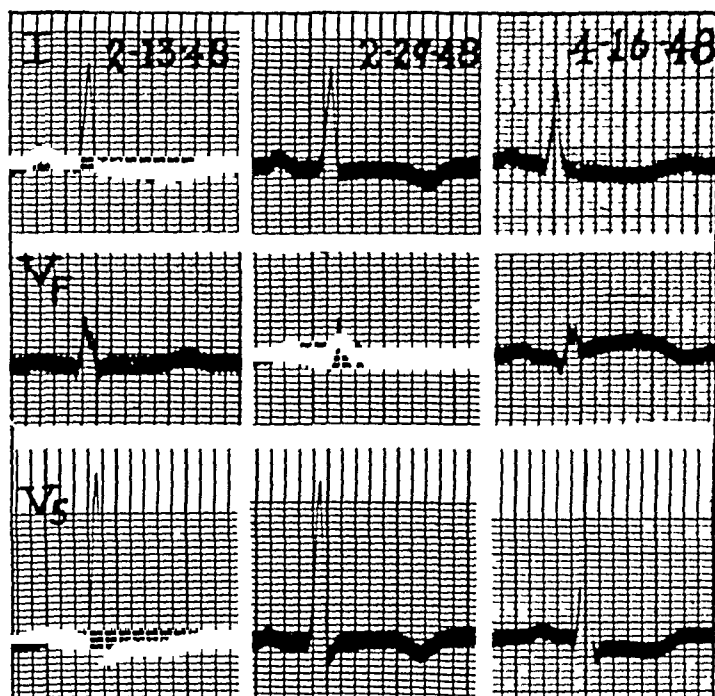


Fig 3—Myocardial ischemia with and without destruction of tissue, illustrated by electrocardiograms in the case of a male laborer of 55 with hypertensive heart disease associated with angina pectoris All leads were taken on each occasion Leads I, V_1 and V_5 , made on Feb 13, 1948, revealed flat T waves with depression of the RT segment when the patient was at rest ("subendocardial ischemia") On February 29, the RS-T segment was normal, but terminal inversion of the T wave was noted ("subepicardial ischemia") On April 16, posterior myocardial infarction occurred (transmural necrosis with "injury" effects—stage 3 in fig 2), leads I and V_5 were then similar to the first record Changes of this type may represent remote effects of the infarction or may indicate additional myocardial ischemia of the anterior endocardial surface of the left ventricle

changes are reversible If a patient in whom only changes in the T wave remain from a previous episode of infarction is again subjected to the

6 Wilson, F N, Johnston, F D, and Hill, I G The Form of the Electrocardiogram in Experimental Myocardial Infarction IV Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *Am Heart J* 10 1025, 1935

insult of ischemia, the pattern will revert to that of a more acute phase (fig 8). It is obvious that such behavior is of prognostic value.⁵

The other changes noted in table 3 are related also to the destruction of body tissue and to the intense inflammatory and regenerative reactions that follow. A sharp reduction in the intensity of the first heart sound often associated with an early diastolic apical gallop rhythm, is commonly noted. Pulsus alternans may be present. If work performance decreases as the result of the injury, the blood pressure falls and the intensity of the second sound likewise diminishes. Fluoroscopic, kymographic and electrokymographic examinations may reveal changes in the cardiac contour with local diminution of cardiac contraction, particularly when the infarcted area involves the lateral cardiac surface

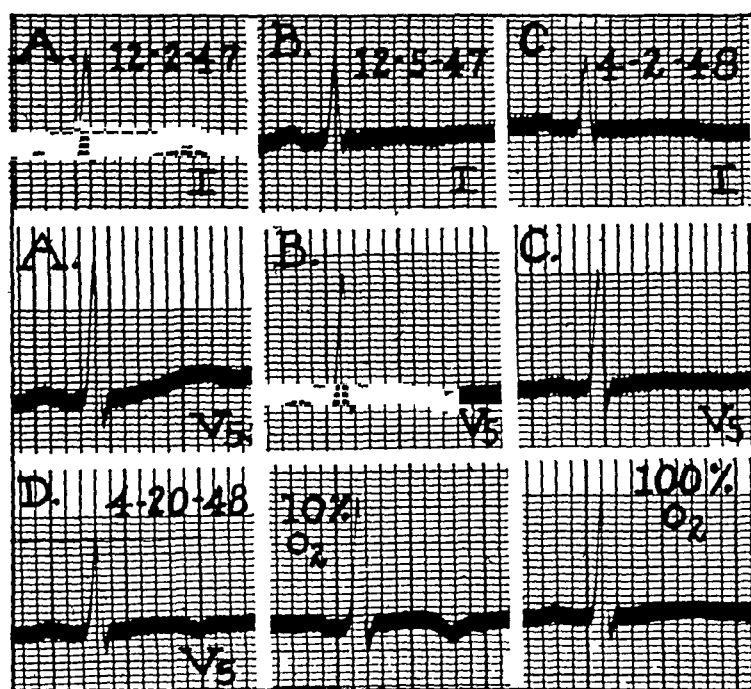


Fig 4—Myocardial ischemia without tissue destruction of the subepicardial type, illustrated by electrocardiograms in the case of a male office worker of 52 with hypertensive heart disease and frequent anginal attacks

On Dec 2, 1947, an essentially normal record was obtained (*A*). On December 5 (*B*), the T wave appeared flat in lead I and showed terminal inversion in lead V_5 , as indicated in *g*, figure 2. On April 2, 1948 (*C*) the record resembled that in *A*. During an anoxia test performed a few days later (*D*), the T wave temporarily reverted to the pattern of *B*, demonstrating that the changes in *B* were apparently caused by myocardial ischemia, presumably of the subepicardial type. The spontaneous changes occurred many times, and the response to the anoxemia test was repeated frequently. Note that no shift in the RS-T segment occurred at any time.

or when the heart is horizontally placed. The intense regenerative reactions result in fever and leukocytosis a few days after the insult. Some associated changes, such as the rise in the sedimentation rate, the temporary increase in the excretion of urobilinogen in the urine

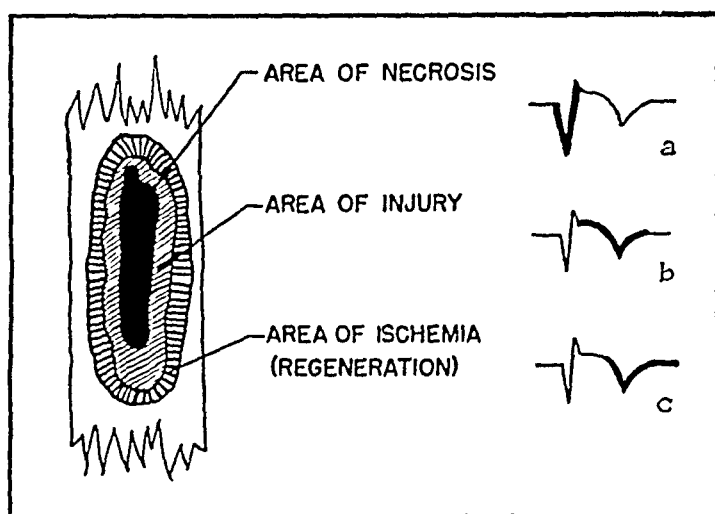


Fig 5—Origin of the components of the electrocardiogram (further explanation in text) The central area of necrosis, an electrically inert region, permits the escape of the potential variation of the endocardium to the surface. As these are primarily negative in an otherwise normally activated heart, deep Q waves occur in surface leads (a). The central region is surrounded by an area that is severely anoxic ("injury") and may or may not be incorporated into the final inert fibrotic scar. As long as this region remains in the injured stage it becomes incompletely depolarized during diastole, which for reasons beyond the scope of this presentation results in elevation of the RS-T segment (b). The outer shell of the infarcted region is less intensely involved. Moderate anoxia of tissue causes a certain delay of repolarization which in leads dominated by this region results in inversion of the terminal portion of the T wave (c). The division is arbitrary and changes with time (fig 6).

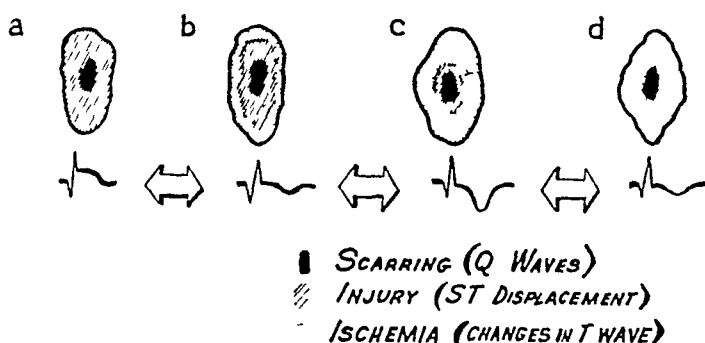


Fig 6—The pattern of myocardial infarction, sequential changes in time and space. The reversible changes of the S-T segment and the T wave may be correlated with the intensity of the ischemia present. As healing progresses the area surrounding the central necrotic region returns to a functional state that approaches the normal (shift from a to d). Additional injury (induced anoxia) may cause a reversal to the acute phase if collateral circulation has not been adequately established (shift from d to a, as shown in figure 8). Solid black indicates necrosis, hatching, severe ischemia ("injury"), and stippling, mild marginal ischemia.

hyperglycemia, glycosuria and certain changes in the protein pattern, may perhaps be regarded as secondary to mild impairment of liver function rather than viewed as a direct result of tissue breakdown

In table 4, the signs of tissue injury are contrasted with those denoting tissue destruction. The subdivision of myocardial ischemia into these two groups has certain advantages over the time-honored division into "angina pectoris," a clinical syndrome, and "coronary occlusion," a pathologic entity. There are intermediate states in which an exact division appears impossible on clinical grounds. A reasonably definite estimate of the functional impairment that has resulted can usually be made if the signs of tissue destruction are contrasted with those denoting injury.

The term "ischemia" [stage 1, fig 2] and "injury" [stage 2, fig 2] are used in a quantitative sense, as in the experiments of Bayley, LaDue and York.⁷ They demonstrated that the various types

TABLE 4—*Signs of Injury and Destruction of Tissue*

Tissue Injury	
Pain	
Changes in terminal portion of T wave ("ischemia")	
Displacement of RT junction ("injury")	
Tissue Destruction	
Increase in body temperature, white cell count,	
sedimentation rate, excretion of urobilinogen	
Decreased R waves, excessive Q waves	

of electrocardiographic changes described by many previous observers are a function of the intensity of the ischemia induced. There is little doubt that this is true for the human heart as well.⁸ If the term "ischemia" is replaced by "repolarization delay" and "injury" by "flow of resting current" or "incomplete repolarization," the concept may be applied to changes in the T wave in general.⁹

7 Bayley, R. H., LaDue, J. S., and York, D. J. Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, *Am Heart J* **27**:164, 1944.

8 Hecht and others.⁵ Johnston, F. D., and Wilson, F. N. Electrocardiographic Findings in the Presence of Myocardial Injury, *Mod. Concepts Cardiovas Dis* **16**: (n p) (June) 1947. Bayley, R. H. An Interpretation of the Injury and the Ischemic Effects of Myocardial Infarction in Accordance with the Laws which Determine the Flow of Electric Currents in Homogenous Volume Conductors, and in Accordance with Relevant Pathologic Changes, *Am Heart J* **24**:514, 1942.

9 Hecht, H. H. On Changes of the T Wave and the RST Segment of the Human Electrocardiogram, *Am Heart J* **37**: 639, 1949.

FUNCTIONAL TESTS

It was stated that myocardial ischemia may be detected at rest only when present in advanced degree. For an objective determination of the "point of tolerance" it is necessary either to decrease the oxygen supply still further or to increase the work performance (table 5). Functional tests devised with this in mind are not without danger, as the point of tolerance should be approached but must not be exceeded. All these tests have the same end point—the production of electrocardiographic changes.

TABLE 5—*Experimental Induction of Myocardial Ischemia*

By decrease in oxygen supply
Anoxic anoxemia
Reflex spasm of coronary arteries (due to cold)
By increase in work requirements
Exercise
Administration of epinephrine

TABLE 6—*Results of 200 Anoxia Tests Performed on 131 Patients*

Diagnosis	Number of Tests	Number of Patients	Result of Test, Percentage of Tests Performed			
			Pain and Electrocardiographic Changes	Electrocardiographic Changes	Pain	No Response
Patient normal	21	21	0	0	0	100
Neurosis (neurocirculatory asthenia)	17	13	0	12	53	,
Myocardial ischemia without tissue destruction (angina pectoris)	94	50	44	31	10	9
Myocardial ischemia with tissue destruction (myocardial infarction)	68	47	28	38	9	25
Totals	200	131	30	30	12 (10.5*)	17†

* Percentage of tests resulting in pain in examples of myocardial ischemia.

† Percentage of tests resulting in last three diagnoses only.

or (much less reliable) the onset of precordial pain or its equivalent. Increase in work performance is difficult to grade and hard to control. An oxygen debt may occur if the point of tolerance is inadvertently exceeded. This cannot be corrected immediately if the patient exercises or if epinephrine has been injected. After some hesitation we have chosen to decrease the arterial oxygen supply artificially by the inhalation of a mixture of 10 per cent oxygen in nitrogen (87 per cent) and carbon dioxide (3 per cent). As oxygen saturation decreases very rapidly during the first five minutes and then remains relatively constant, definite evidence of myocardial ischemia is usually obtained during the first ten minutes of the test. It is never carried over twenty minutes. If the

test is modified from the original description by Levy and others¹⁰ to include a number of unipolar limb leads and precordial leads and if the test is evaluated in accordance with the patterns illustrated in figure 2 rather than by using arbitrary standards, a great deal of information may be obtained.⁶ The experimental procedure allows the subject to be outwardly at rest in the recumbent position, which greatly facilitates the study of such patients. It permits instantaneous administration of 100 per cent oxygen as soon as the point of tolerance is reached. No oxygen debt is encountered, and the lowered arterial oxygen saturation, which in Salt Lake City amounts to 75 per cent of normal, is corrected within one minute. The addition of carbon dioxide eliminates many objections that have recently been raised by tending to establish a uniform respiratory rate and depth. No lasting adverse reactions were encountered in over 300 tests, two thirds of which were performed on patients with myocardial ischemia with and without destruction of tissue. Table 6 gives the over-all results of the test in the first 200 instances, table 7

TABLE 7—*Practical Value of the Anoxia Test*

Differential diagnosis of precordial pain
Estimation of "point of tolerance"
Estimation of rate of recovery (prognosis)
Estimation of therapeutic procedures

illustrates how such a functional approach may be of value in evaluation of the diagnosis, therapy and prognosis of myocardial ischemia.

PROGNOSIS

From the clinical course in cases of advanced degrees of myocardial ischemia, and by the use of a functional approach only, as outlined, it became apparent that the prognosis in such cases does not depend on the location or the severity of the original insult but on (a) the size and penetrance of the lesion and (b) the speed and efficiency with which collateral circulation develops. In severe ischemia with or without destruction of tissue, the size of the lesion can be estimated from the number of precordial and esophageal leads involved in the process. When the changes are confined to the R-T segment and the T wave but other signs pointing to destruction of tissue are noted, nonpenetrating myocardial infarction may be present. Such infarcts are benign when they involve the epicardial surface, they are almost always fatal when they spread endocardially. In general, of course, the more severe the degree of ischemia and the more extensive the involvement of the heart

10 Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A. The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, *Am Heart J* **21** 634, 1941.

muscle in the process, as estimated from the electrocardiogram, the poorer the outlook, yet, there are significant exceptions. There are patients who display severe ischemia with injury, as demonstrated by upward displacement of the R-T junction, continuously for months and years. An extreme example of this kind is illustrated in figure 7. In this case, severe myocardial ischemia of the "injury" type (stage 2, fig 2) was present over a four year period. Katz described similar instances.¹¹ The changes in such patients depend on the presence of a severely ischemic region which fails to improve but is also not converted into inactive scar tissue. Such records are usually the result of extreme

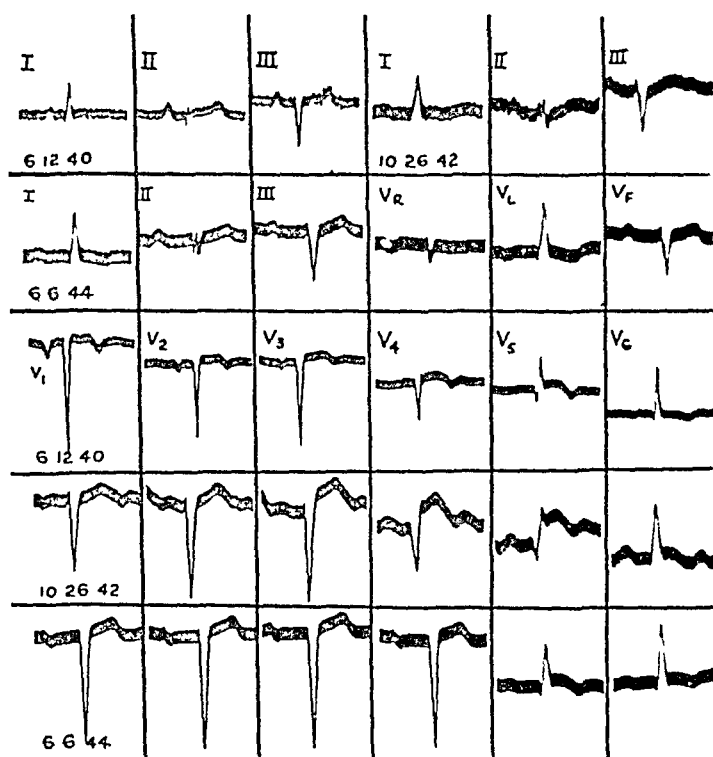


Fig 7—Unretouched tracings (time lines omitted by overexposure) showing prolonged myocardial injury with permanent elevation of the S-T segment in the case of a female infirmate of 65 with frequent attacks of angina pectoris. Precordial leads taken over a four year interval regularly display a pattern suggestive of "recent" myocardial infarction. It is assumed that inadequate collateral circulation arrested the usual electrocardiographic evolution at stage *b* of figure 6. Similar cases of much shorter duration were reported by Katz¹¹ and Wilson and others (*Am Heart J* 27:62 [fig 25], 1944).

ischemia caused by an almost complete occlusion of a coronary artery with a pinpoint lumen. A trickle of blood rinsing such regions apparently interferes with the development of an adequate collateral circula-

11 Katz, L. N. *Electrocardiography*, ed 2, Philadelphia, Lea & Febiger, 1946, p 369.

tion If, on the other hand, in subjects recovering from the effects of myocardial infarction the pattern of the electrocardiogram as illustrated in figure 6 reverts from stage *d* to stage *b*, it is assumed that new injury has occurred or that an extension of the infarcted region has taken place. If it occurs spontaneously it must be regarded as an ominous sign. It may be experimentally induced in patients who have recovered and are subjected to an anoxia test. The temporary reversal during induced hypoxia twenty-five days after an episode of myocardial infarction in a woman of 69 is illustrated in figure 8. The reappearance of the pattern of acute injury during the test indicates that an adequate collateral circulation has not been fully developed. In such patients, the point of tolerance is, therefore, easily exceeded, and the activities of subjects displaying such a reaction should be severely restricted. In other cases, no changes occur during the test, as early as one month after the original insult. It may be assumed that adequate collateral circulation has been established. It is suggested that such a functional approach may be of help in the evaluation of the disorders and in the rehabilitation of sub-

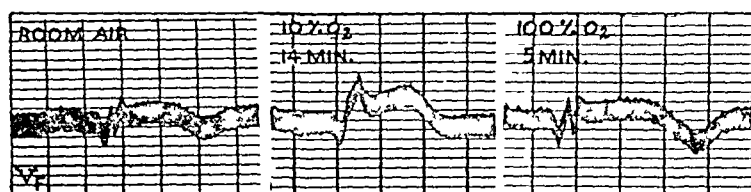


Fig 8—Response to induce anoxia in myocardial infarction in the case of a housewife of 69. Myocardial infarction occurred four weeks prior to the anoxia test. No pain was signaled, but the response reverted from stage *d* to stage *b* of figure 6, suggesting incomplete revascularization of the area surrounding the infarct. (Only lead V_F is reproduced)

jects who have suffered from one or more episodes of myocardial infarction. It is for this reason that the anoxia test has become a standard procedure in our patients with myocardial infarction on discharge from the hospital and at regular periods thereafter. In some instances, we have found that the original ischemic area remained unchanged during the test but that areas remote from the original site responded with an ischemic pattern. This response may point to the existence of additional regions with impaired blood supply. The prognosis should be guarded for such patients and their activity restricted.

It is fortunate that even in a normal heart an abundant collateral circulation exists. It remains dormant until a sudden obstruction of a major pathway permits the opening of preformed collateral channels.⁴ A gradual reduction in arterial blood supply is apparently a much less efficient stimulus than sudden cessation of flow. Consequently, some patients with myocardial ischemia with destruction of tissue appear to tolerate the effects of anoxia better than subjects who suffer from

ischemia without destruction. This clinical impression is supported by the observation that 25 per cent of the patients for whom the test was performed from a few weeks to a few months after the infarction showed neither electrocardiographic nor subjective evidence of further impairment during the test, while this was true of only 9 per cent of patients with apparent ischemia but without infarction (table 6).

The importance of an adequate collateral circulation is demonstrated by 2 examples (fig 9). In both cases, complete occlusion of the descending branch of the left coronary artery was demonstrated at autopsy. A

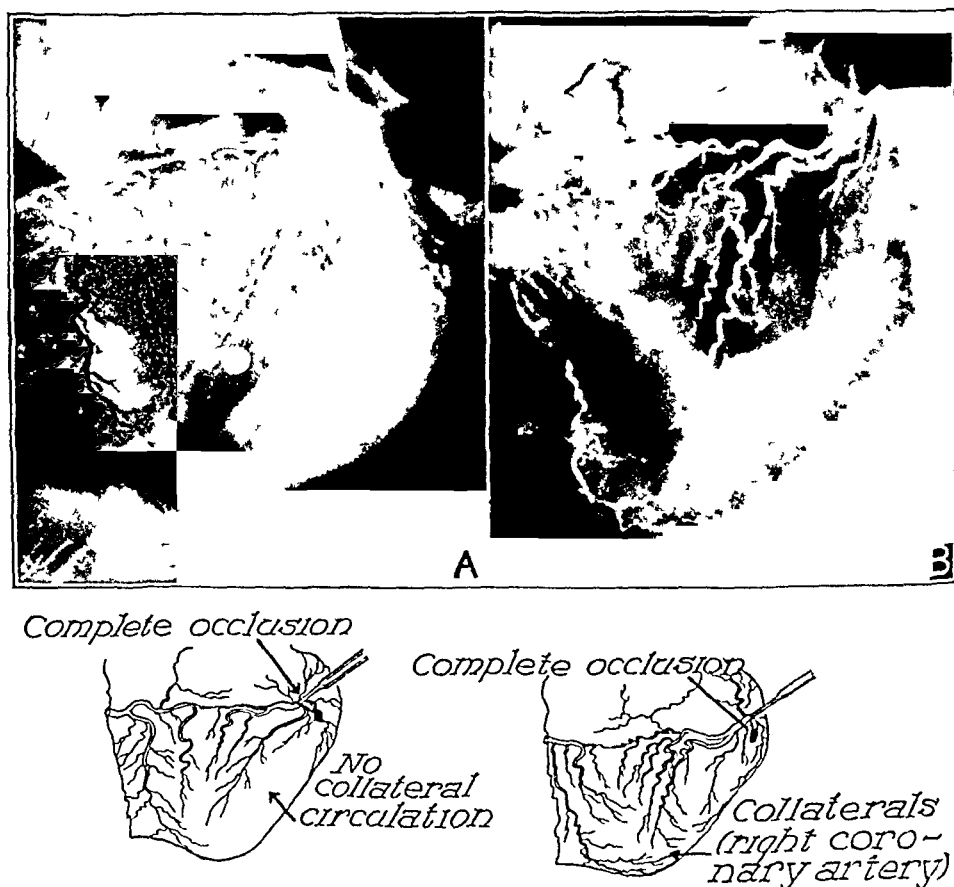


Fig 9—Spontaneous revascularization in myocardial infarction. Two examples of complete occlusion of the anterior descending branch of the left coronary artery are compared (further explanation in text). The hearts were injected and dissected according to the method of Schlesinger. In B, all visible vessels beyond the point of occlusion were filled by the injection mass introduced into the right coronary artery, showing adequate collateral circulation. The right ventricle filled normally in both cases (compare with Blumgart, H. L., Schlesinger, M. J., and Davis, D. *Am Heart J* 19 1, 1940).

The white dots in A represent, from right to left, the positions for precordial leads V_4 , V_5 and V_6 .

woman of 76 (fig 9B) survived the insult and succumbed many years later to lobar pneumonia. The other patient, a man of 56 (fig 9A), died in heart failure three weeks after the attack. It can be seen clearly

that in the first patient adequate filling of the region usually supplied by the left coronary artery had been accomplished from the opposite side. The heart was functionally competent, and with the exception of a scar the effect of the ischemia had been completely overcome. In the second case, compensatory adjustments failed and a large, completely ischemic region involving major portions of the left ventricle led to intractable heart failure and to death. It is clear that a functional test from which conclusions may be drawn regarding the adequacy of the collateral circulation following a major attack of ischemia should prove to be a valuable tool in the guidance of such patients.

TREATMENT

In the first case (fig 9B), no specific treatment was instituted. In fact, the attack was not recognized, yet, a functionally adequate result

TABLE 8—*Treatment of Myocardial Ischemia*

Increase in oxygen supply
Administration of oxygen
Administration of nitrites
Parenteral administration of aminophylline
Administration of alcohol (large doses of papaverine [?]) and possibly of khellin)
Correction of underlying associated diseases
Decrease in work performance
Sedation
Relaxation
Active decrease in metabolism

ensued. Minor degrees of ischemia secondary to changes other than those occasioned by diseases of the coronary arteries usually are relieved on recovery from the initiating process. As demonstrated, complete occlusion of a coronary artery is also not infrequently followed by adequate functional recovery. It is less well recognized that patients with ischemia due to narrowing of the coronary arteries (or with angina pectoris) in the main also improve spontaneously or on the institution of a few simple measures (table 8). Unless carried out over long periods of time, the evaluation of agents alleged to cure angina pectoris is extremely difficult. At present, it may be said that quick-acting vasodilators are certainly beneficial in the acute attack. Unless they decrease peripheral resistance precipitously, they tend to increase the oxygen supply to the heart muscle. If they are frequently taken and if at the same time the work requirements of the heart muscle are reduced by sedation, purposeful rest or, in an occasional case, by decreasing metabolic requirements with thiouracil derivatives, the discrepancy between oxygen supply and work requirements may be overcome and the patient restored to a useful life.

There are no agents or practical procedures, however, that will consistently promote collateral circulation, increase oxygen uptake of the heart or otherwise correct the results of the discrepancy between oxygen supply and work requirements. It is significant that when such substances are introduced it is stated that treatment is to be continued for months at a time. During such prolonged periods of observation spontaneous improvement is likely to be observed, particularly if the patient has been instructed carefully to record the frequency of his attacks and the number of glyceryl trinitrate tablets consumed. This leads the patient to discover the factors in exceeding the point of tolerance which cause an increased demand for vasodilators. Such efforts will be consciously or unconsciously avoided. If it is insisted that no treatment other than mild sedation and the administration of glyceryl trinitrate be instituted for several months before the patient is placed on a new form of treatment, and if the patient is asked to chart his course carefully, spontaneous "improvement" is the rule rather than the exception. In spite of apparent improvement, in some cases the response to the anoxia test remains unaltered over the years. This implies that in these subjects collateral circulation has not appreciably increased but that the patient has learned to reduce his activity to below the point of tolerance. In other examples, actual improvement may be demonstrated by the patients' increased tolerance to artificially induced hypoxia. In either case, it may be said that myocardial ischemia shows an inherent tendency to spontaneous improvement in the majority of patients who adjust their activities to their disease.

SUMMARY

1 Many factors upset the balance between oxygen supply and work requirements of the heart muscle. This results in general or local myocardial ischemia. Diseases of the coronary arteries are the most important but not the only factors leading to the appearance of the syndrome.

2 The syndrome of myocardial ischemia is characterized by pain, electrocardiographic changes and certain remote reactions secondary to tissue destruction. Pain is an unreliable guide. The electrocardiographic changes are manifold and in the less severe stages involve only the S-T segment and the T wave. They are determined by the intensity of the process and by the location of the lesion with respect to the recording electrodes. "Delay of repolarization" involves the T wave proper, "incomplete repolarization" (with flow of resting currents during diastole) modifies the RS-T segment. The direction of the changes with respect to the isoelectric base line of the electrocardiogram is determined by the location of the predominantly ischemic region. "Subendocardial" and "subepicardial" involvement may thus be contrasted.

3 In myocardial infarction, the signs of gross tissue destruction are added to those of myocardial ischemia. It is therefore suggested that the term "myocardial ischemia without tissue destruction" be used to define angina pectoris and "myocardial ischemia with tissue destruction" to denote myocardial infarction. The new terms allow an estimation of the functional impairment of intermediate clinical states in which the diagnosis of "severe angina pectoris" or "coronary occlusion" cannot be made with certainty.

4 The "point of tolerance" defines the limits of cardiac reserve. In decompensated ischemia, the signs and symptoms appear when the patient is at rest. If an appreciable cardiac reserve is still available, an objective diagnosis can only be made by appropriate functional tests. The inhalation of a mixture of a small amount of oxygen with nitrogen and carbon dioxide in conjunction with a detailed electrocardiographic examination is suggested as a useful and relatively harmless procedure.

5 Alterations in the electrocardiogram during the test in patients who have suffered an episode of myocardial infarction depend largely on the degree of revascularization. The result of the test in such patients may allow certain limited prognostic conclusions.

6 Myocardial ischemia from any cause tends to improve spontaneously in many instances. Under palliative treatment, the majority of patients may be returned to a useful life once they have learned to adjust their activities to their limitations.

EXCRETION OF CHOLINE IN THE URINE OF DIABETIC PATIENTS

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THE IMPORTANCE of choline as a dietary factor was first detected in depancreatized dogs which were given insulin over a long period. It was found that choline was able to inhibit the development of fatty liver in such animals¹. Later it was shown that choline is generally an essential dietary factor, playing an important role in fat metabolism². As diabetes mellitus represents a disease with disturbances not only in the carbohydrate metabolism but also changes in the fat and protein metabolisms, it can be assumed that in this case also the choline plays some part after acting as a general regulator in the fat metabolism. It was shown by Conte-Marotta³ that choline given orally in large dosage is able to decrease the rate of development of ketone bodies in white rats with phlorhizin diabetes. Paul, Daum and Kemp,⁴ on the other hand, were able to show that hyperlipemia in diabetes mellitus disappears after administration of choline. Pelner, Davidson, Waldman and Margolis⁵ reported that 18 diabetic patients were successfully treated with choline, whereas 8 did not respond to the medication.

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1 Best, C. H., Ferguson, G. C., and Hershey, J. M. Choline and Liver Fat in Diabetic Dogs, *J. Physiol.* **79** 94-102, 1933

2 (a) Best, C. H., and Lucas, C. C. Choline—Chemistry and Significance as a Dietary Factor, in Harris, R. S., and Thimann, K. V. *Vitamins and Hormones. Advances in Research and Applications*, New York, Academic Press, Inc., 1943, vol. 1, pp. 1-58. (b) Jukes, T. H. Choline, *Ann. Rev. Biochem.* **16** 193-222, 1947

3 Conte-Marotta, R. Influenza della colina sulla chetonuria, *Arch. di sc. biol.* **24** 396-398, 1938

4 Paul, W. D., Daum, K., and Kemp, C. R. The Action of Choline on the Blood Lipid Fractions in Cirrhosis of the Liver, Diabetes Mellitus and Related Conditions of Disturbed Fat Metabolism, *J. Iowa M. Soc.* **37** 146-155, 1947

5 Pelner, L., Davidson, B., Waldman, S., and Margolis, R. The Role of Choline Chloride in the Treatment of Certain Cases of Diabetes Mellitus, *New York State J. Med.* **48** 523-524, 1948

Little is known about the choline metabolism in diabetic patients. Lindberg and Mollerstrom⁶ found an increased excretion of choline in the urine of some diabetics. They used the periodate precipitation method of Roman⁷ for the analyses. This method is known to possess very little accuracy, giving values that are too high and uncertain even in normal subjects. In the study of the metabolism of choline in diabetic patients, we first investigated the urinary excretion of choline by a more accurate and sensitive method.

EXPERIMENTAL STUDY

Method—A quantitative estimation of choline in biologic materials can be made only by means of an accurate method which is highly sensitive and specific. The known chemical methods are unsatisfactory in this respect. They have been discussed and criticized in detail by Best and Lucas^{2a} and by Borglin.⁸ The latter carried out careful investigations with the urine of white rats and of man on a large scale and found that only the biological methods can be used for investigations of this type. Schlegel⁹ investigated the choline content of the blood in man and arrived at the same conclusion.

The principle of this method is the acetylation of the choline into the more active acetylcholine and determination of the latter by pharmacologic titration. In the course of this work we selected the biologic method using surviving rabbits intestine for estimation of the acetylcholine. The experiments were carried out mainly in accordance with the description given by Borglin,⁸ with slight modifications as described below.

Preparation of Urine The preparation of the urine samples and the acetylation were carried out exactly according to the technic mentioned. Twenty-four hour samples were collected under toluene from both diabetic and normal persons, the p_H made acid to litmus and 10 cc samples taken for analysis. The urine was treated with alcohol, centrifuged and the water-alcohol solution evaporated under reduced pressure at 80 to 90 C to about 0.5 cc. To the residue, 15 cc of acetic anhydride was added and refluxed on a water bath for twelve minutes (Abdon and Ljungdahl-Ostberg¹⁰). The excess of acetic anhydride was

6 Lindberg, O., and Mollerstrom, J. Ueber Cholinausscheidung bei Diabetes mellitus, *Naturwissenschaften* **31** 65-66, 1943.

7 Roman, W. Eine chemische Methode zur quantitativen Bestimmung des Cholins und einige physikalisch-chemische Daten des Cholins und seiner Salze, *Biochem Ztschr* **219** 218-231, 1930.

8 Borglin, N. E. On the Excretion of Choline in Urine, *Acta pharmacol et toxicol* (supp 1) **3** 1-123, 1947.

9 Schlegel, J. U. Variationer i serumcholinindholdet hos mennesker, Copenhagen, Ejnar Munksgaards Forlag, 1948.

10 Abdon, N. O., and Ljungdahl-Ostberg, K. A Method for Quantitative Determination of Acetylcholine Precursor and Free Acetylcholine in Tissues, *Acta physiol Scandinav* **8** 103-121, 1944.

distilled off at reduced pressure to about 1 cc. The remaining solution was diluted with several cubic centimeters of distilled water, and the acetic anhydride was removed by means of repeated washing with ether. Finally distilled water was added to the samples until the volume amounted to 15 cc, and they were kept in a refrigerator at -20°C until the biologic estimation was made.

Preparation of Food Samples Extraction and acetylation of total choline in food was carried out according to the description given by Fletcher, Best and Solandt¹¹. A daily diet for one person was collected, minced and mixed very carefully, the whole amount weighed and 50 Gm taken for analysis. The sample was refluxed with 500 cc of 18 per cent hydrochloric acid for one hour. After cooling, the mixture was made up to 1,000 cc and filtered and 10 cc treated in the same way as the urine.

Estimation of Choline The biologic estimation was carried out with rabbit intestine. The animals were killed after being kept for twenty-four hours without food, the duodenum and the upper part of the jejunum were taken out immediately after killing, washed and kept in a refrigerator for twenty-four hours in a physiologic solution of the following composition:

	Gm or Cc
Sodium chloride	80
Potassium chloride	02
Calcium chloride (anhydrous)	02
Magnesium chloride (anhydrous)	01
Twice distilled water to make	1,000 0

A piece of intestine 10 to 15 mm long was placed in a 50 cc Magnus vessel which was mounted in a water bath at temperature of 38°C . The Magnus vessel contained the same physiologic solution with 1 Gm of dextrose and 1 Gm of sodium bicarbonate added to each liter. A mixture of 93.5 per cent oxygen and 6.5 per cent carbon dioxide was bubbled through the solution. The contractions of the intestine were registered on a suitable kymograph.

The titration of acetylcholine in the sample was carried out in the following way. The addition of a given amount of the test solution caused a contraction, the height of which was just between the heights of contractions caused by two different known amounts of acetylcholine. The standard solution of acetylcholine used was freshly prepared and contained 1 microgram to each cubic centimeter. Attention was paid to the fact that increasing amounts of acetylcholine produce different contractions, the heights of which give an asymptotic curve. The amounts of test solution and acetylcholine standard solution were therefore selected so that the height of the contractions came within the rising part of this asymptotic action curve. In this way it was easy to obtain the actual rates by simple interpolation. Each amount of known and unknown acetylcholine solution was added at least twice and mean values taken. After each application of standard and test solutions, the intestine in the Magnus vessel was washed twice with the physiologic solution at 38°C .

Accuracy of Estimate The accuracy of the method was controlled in different ways. In some experiments two parallel samples, each of 10 cc, were taken from the same urine, acetylated and examined separately with different intestines. The results are given in table 1. It will be seen that the highest difference between two parallel estimations

¹¹ Fletcher, J. P., Best, C. H., and Solandt, O. M. The Distribution of Choline, *Biochem J* **29** 2278-2284, 1935.

is about 15 per cent. The other question as to the accuracy of the method is whether the choline in the urine samples is completely converted into acetylcholine. This problem was investigated in the following way. A 10 cc sample of urine was acetylated and the acetylcholine estimated. Then known amounts of choline hydrochloride were added to the same urine and the estimation repeated. The results, given in table 2, show the acetylation to be complete.

Results—The subjects used in these experiments were given the same hospital diet. This was plentiful (over 3,000 calories daily), and in most cases it was not completely consumed. The total choline content of the daily diet was estimated for two days. The results are given in table 3. A corresponding value could be obtained also by simple com-

TABLE 1—*Values Obtained in Parallel Estimations of Choline Content in 10 Cc Samples of Urine*

Experiment	Choline Content, Micrograms		Difference	
	No. 1	No. 2	μg	Percentage
1	11.4	11.2	0.3	2.7
2	47.2	43.0	4.2	9.8
3	20.0	17.3	2.7	15.5

TABLE 2—*Determination of Choline Content When a Known Amount of Choline is Added to a 10 Cc Sample of Urine*

Choline Chloride, Micrograms		Difference Between Calculated and Found	
Added	Found	μg	Percentage
0.0	42.1		
10.0	57.5	5.4	9.4
30.0	78.0	5.9	12.2

putation on the basis of the table given by Borglin,⁸ presenting the choline content of the most usual Swedish foods. The choline content of the hospital diet according to this table was calculated for six consecutive days and values from 280 to 780 mg. a day (average 520 mg. a day) were obtained.

Borglin found that the ordinary Swedish hospital diet contains between 300 and 500 mg. of choline daily, on occasional days up to 800 mg. Our own results tally with these figures. Furthermore, Borglin found in investigations on many healthy subjects in Sweden that the daily choline excretion in the urine corresponds to about 0.5 to 1 per cent of the total choline consumed with the food. Regarding these results of Borglin's and our own results given in table 3, it can be assumed that for the patients examined by us normal rates of choline excretion are 5 mg. or less, whereas values over 50 mg. indicate

increased choline excretion Table 4 shows the results of estimations of choline in the daily urine in some diabetic patients and in healthy persons on the same diet It will be seen that in some cases the amount of choline in the daily urine is much higher than the 50 mg mentioned, in other cases it is within normal limits The healthy subjects excreted less than 50 mg of choline daily When the ratio of the excreted choline to the choline consumed with the food is computed as a percentage (on the basis that about 500 mg of choline is consumed with the food

TABLE 3—*Choline Content of Daily Hospital Diet*

Days	Choline Content (Bound + Free), Mg	Mean Value, Mg
10/29/48	605 0 660 0	632 5
10/30/48	488 0 440 0	464 0
		548 3

TABLE 4—*Excretion of Choline in Urine of Diabetic and of Normal Subjects for Three Consecutive Days*

Subject	No 1	No 2	No 3
Diabetic			
H J	10 30 (2 1)*		
D C O	14 45 (2 9)		
L K A	18 80 (3 8)		
J A	2 12 (0 4)		
G S R		3 90 (0 8)	3 10 (0 6)
S D J		3 10 (0 6)	4 15 (0 8)
C G		4 55 (0 9)	2 82 (0 6)
K O	0 61 (0 1)		
G A		2 75 (0 6)	2 80 (0 6)
H S		6 30 (1 3)	1 40 (0 3)
D G		1 83 (0 4)	
B G			5 20 (1 1)
Normal			
O S		2 91 (0 6)	3 80 (0 8)
T C			2 22 (0 4)

* Figures in parentheses represent the ratio between consumed and excreted choline expressed as a percentage on the assumption that 500 mg of choline is ingested with the food daily

daily), the values for diabetic subjects are 0 1 to 3 8 per cent and for healthy subjects 0 4 to 0 8 per cent As previously mentioned, the physiologic values range up to 1 0 per cent It will be seen also from table 4 that the amount of choline in the daily urine is not stable Furthermore, it varies so much that it is difficult to obtain a true picture of the choline excretion when only the values for one or two days are considered Therefore, it was necessary to follow the daily urinary excretion in diabetic and in normal subjects for several days to obtain more figures for statistical evaluation Table 5 presents the values obtained in experiments of this type The figures shown in table 5 were

evaluated statistically and the significant differences between the values for each subject are given in table 6. As to the tables 5 and 6, the diabetic subjects can be divided into two groups. One group (patients J A and B A) had choline excretion which corresponds to the normal

TABLE 5—*Urinary Excretion of Choline by Diabetic and by Normal Subjects Over a Period of Several Days*

Subject	Sex	Age, Yr	Type of Diabetes*	Choline Excretion, Mg per Day									
Diabetic													
J A	F	68	B	2.91	2.12	0.90	1.70	2.03	1.76	2.68	3.63	2.22	
B A	M	45	A	3.22	1.30	1.08	2.32	2.63				2.12	
H I	F	69	B	7.40	6.05	5.00	10.30	61.0	8.60	8.26		7.40	
N C	M	42	B	11.88	7.65	10.34	6.76	6.16	10.67			8.92	
L K A	M	69	A	5.30	4.90	4.90	18.80	9.50	10.00	12.00	18.15	10.44	
D K O	M	38	A	3.60	6.89	11.34	14.48	20.00	20.93	10.33	11.32	12.35	
Normal													
D J	M	35		0.82	1.25	1.90	1.85					1.46	
N N	M	42		1.20	1.65	1.50	2.30					1.66	
L G	M	50		1.65	1.70	1.76	2.40					1.88	

* Type A indicates diabetes with excretion of ketone bodies, type B, diabetes without excretion of ketone bodies

TABLE 6—*Mean Values (M), Standard Error of Mean Values (μx) and Significant Differences*

Subject	M	μx *	Significant Differences†								
			J A	B A	H I	N O	L K A	D K O	D J	N N	L G
J A	2.22 ± 0.284			0.20	5.19	6.15	4.19	4.90	1.99	1.61	1.04
B A	2.12 ± 0.412		0.20		5.06	6.03	4.19	4.90	1.36	1.01	0.54
H I	7.40 ± 0.957		5.19	5.06		1.07	1.40	2.19	6.00	5.88	5.69
N O	8.92 ± 1.048		6.15	6.03	1.07		0.61	1.50	6.92	6.81	6.62
L K A	10.44 ± 1.940		4.19	4.19	1.40	0.61		0.68	4.85	4.48	4.38
D K O	12.35 ± 2.046		4.90	4.92	2.19	1.50	0.68		5.29	5.19	5.10
D J	1.46 ± 0.254		1.99	1.36	6.00	6.92	4.85	5.29		1.92	1.39
N N	1.66 ± 0.199		1.61	1.01	5.88	6.81	4.48	5.19	1.92		0.85
L G	1.88 ± 0.165		1.04	0.54	5.69	6.62	4.38	5.10	1.39	0.85	

$$* \mu x = \frac{\left(\frac{\sum \Delta x}{n} \right) 1.25331}{\sqrt{n}}$$

$$† \text{ Significant difference} = \frac{M_1 - M_2}{\sqrt{\mu x_1^2 + \mu x_2^2}}$$

Values above 4.00 are considered statistically significant

The significant differences between the values for daily choline excretion in these patients and those in normal subjects are 1.99, 1.61, 1.04 and 1.36, 1.01, 0.54 respectively. This means that there is a full agreement between the two groups regarding the choline output. In the other 4 diabetic subjects the rate of choline excretion is higher than normal.

The difference between the two groups is significant statistically in each case, as the values for significant differences are always above 4.00

COMMENT

The accuracy of the biologic method of choline estimation has been established by several investigations (Best and Lucas,^{2a} Borglin⁸ and Schlegel⁹), and in our own experiments it was also shown to be reliable, giving true values for the choline content of the urine. As mentioned in the introduction, the aim of this investigation was to obtain an idea as to the choline metabolism in diabetic persons. Very little is known about what happens to choline consumed with the food. It is certain that the choline comprised in the daily diet plays an important part in the fat metabolism, it becomes a part of the lecithin molecule and is partly converted into dimethylaminoethanol, yielding a labile methyl group, and partly oxidized to betaine aldehyde and betaine, but neither its ultimate fate nor the connection between these reactions is completely known. About 0.5 to 1.0 per cent of the choline consumed with the food is excreted unchanged in the urine, whereas 99.0 to 99.5 per cent takes part in the metabolism on other routes. Therefore, if one intends to study the metabolism of choline in diabetic subjects, it is first necessary to investigate the per cent ratio between the choline consumed and that excreted in these subjects.

As a basis for calculation of the excretion of choline in healthy subjects who eat ordinary Swedish food, we took Borglin's results supplemented by some investigations carried out by us. Borglin made many investigations regarding the choline content of foodstuffs and the choline excreted in the urine and found that the usual Swedish diet contains on an average 300 to 500 mg of choline daily. Normal healthy persons consuming the common Swedish diet eliminate choline in the urine in amounts varying from 2 to 4 mg daily, in occasional cases only is this average a little higher. These figures represent about 0.5 to 1.0 per cent of the daily choline intake.

The diabetic patients in our hospital had generally had a diet composed of the usual Swedish food, without restrictions as to amount and composition. The amount of choline in a daily portion of this food according to our analyses averaged 564 mg, which represents the highest figure possible, as maximum amounts of food were used for choline estimations. These amounts could usually not be consumed by the patients. By way of control, healthy subjects without metabolic disorders were selected, some of whom were given the same diet, while others ate ordinary Swedish food outside the hospital. All the normal subjects showed an excretion lower than 1 per cent of the daily choline intake. On the average, the values were not higher than 4 mg, and all were lower than 5 mg.

It seems also that under physiologic conditions, the choline output shows only a small variation up to 5 mg daily. Values averaging over 5 mg can be taken to indicate an abnormal choline metabolism.

In some diabetic patients¹² we found the choline excretion to be increased for several days, and in this case the means were higher than 5 mg. The difference between the figures obtained for these patients and those obtained for normal subjects was also statistically significant. This means that in such cases one is obliged to assume a pathologic choline metabolism. On the other hand, we found a normal choline output in some diabetic patients, and the figures also agree statistically with those for normal subjects. Our experiments were too few to permit a statement about the percentage of diabetic persons with an increased choline output, nor can we give an opinion about the relation between the level of choline excretion and clinical symptoms of diabetes mellitus. It seems, however, that in the cases investigated no relations obtained between the choline output and the excretion of ketone bodies. This observation needs further confirmation. Also, the question of the influence of insulin on the choline excretion in the urine of diabetic persons needs further investigation.

SUMMARY

The daily choline excretion in the urine was investigated in diabetic and in healthy subjects. The estimation of choline was carried out by acetylating the choline and estimating the acetylcholine with surviving rabbit intestine. In healthy subjects values up to 5 mg per day were noted, whereas in some persons with diabetes mellitus the choline output was found to have increased and showed a statistically significant difference from the values for normal subjects. No correlation was found to obtain between the level of choline excretion and diabetic symptoms. The importance of an increase in choline excretion as a symptom of disorders in the choline metabolism is discussed.

¹² The sodium sulfosalicylate test for albumin in the urine used in this investigation gave negative results in all the diabetic patients.

MULTIPLE HEMORRHAGIC SARCOMA AND DIABETES MELLITUS

Review of a Series, with Report of Two Cases

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MULTIPLE idiopathic hemorrhagic sarcoma is a chronic disease with characteristic cutaneous lesions and, occasionally, widespread internal involvement. It was first described by Kaposi in 1872, and, although the disease is relatively rare, the literature on the subject has been copious. Kren¹ wrote a 113 page monograph with 10 pages of references, and twenty-four synonyms have been listed for the disease. In 1932, Dorfell² searched the literature and found reports of 356 bona fide cases, of which only 21 had occurred in females. Choisser and Ramsey,³ in 1939, stated that 600 cases had been reported since 1872. Persons of Jewish extraction are particularly though not exclusively affected, and most patients come from Russia, Poland, or Italy and are of the laboring class. Lowenthal,⁴ in 1938, recorded a case in a full-blooded Negro and stated that only 3 similar cases had been reported previously, Persky and Lisa⁵ reported another in 1944.

The disease generally appears after the age of 40, and the highest incidence is in the sixth and seventh decades of life, but it occurs in younger age groups. Denzer and Leopold⁶ reported a fatal case in a

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1 Kren, O, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1933, vol 12, pt 3, pp 891-1004.

2 Dorfell, J. *Histogenesis of Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi*, *Arch Dermat & Syph* **26** 608-634 (Oct) 1932.

3 Choisser, R M, and Ramsey, E M. *Angioreticuloendothelioma (Kaposi's Disease of the Heart)*, *Am J Path* **15** 155-178 (March) 1939.

4 Lowenthal, L J A. *Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi*, *Arch Dermat & Syph* **37** 972-974 (June) 1938.

5 Persky, B P, and Lisa, J R. *Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi in a Full-Blooded Negro*, *Arch Dermat & Syph* **49** 270-272 (April) 1944.

6 Denzer, B S, and Leopold, H C. *Idiopathic Hemorrhagic Sarcoma (Kaposi)*, *Am J Dis Child* **52** 1139-1147 (Nov) 1936.

child of 4½ MacKee and Cipollaro⁷ stated that the duration of the disease ranges from one to twenty-five years but that the average patient survives only five to ten years, and that death is often attributable to hemorrhage and emaciation from visceral involvement

The initial lesions commonly appear on the extremities (especially the legs) as reddish or purplish nodules of firm consistency which may coalesce into infiltrated plaques. Later lesions may appear anywhere on the skin and sometimes on mucous membranes. Pautrier and Diss⁸ described a case in which the lesions began as small, colorless, painful hypodermal nodules which were detected only by palpation and later assumed the characteristic violaceous hue. However, the early cutaneous lesions are almost always visible and are not ordinarily painful. In the case reported by Jessup,⁹ the only detected lesions were on the scalp and forehead, and sections showed cells invading the lumen of a large vein.

Autopsies have frequently shown that almost any organ may be invaded. In a number of instances, there has been visceral involvement without any demonstrable changes in the skin. Choisser and Ramsey³ described 2 curious cases without cutaneous lesions in which tumors located within the right auricle caused a ball valve type of obstruction at the tricuspid orifice which was rapidly fatal. Aegerter and Peale¹⁰ recorded a case in which death resulted from a 1,000 cc tamponade due to hemorrhage and stated that when the disease was primarily of the viscera it was usually not present in the skin. Nesbitt and others,¹¹ in 1945, observed disseminated lesions in a fatal case without cutaneous involvement and noted that in no previously reported case had a patient shown lesions of the brain and the thyroid gland. Dorfell² mentioned that the pancreas is not infrequently involved.

Kaposi's sarcoma and the lymphomas occasionally appear together, as in the case of Sachs and Gray,¹² in which lesions of Kaposi's sarcoma were noted in the upper cutis and an infiltrate of lymphatic leukemia was evident in the lower cutis. Death was attributed to the leukemia. In

7 MacKee, G. M., and Cipollaro, A. C. Idiopathic Multiple Hemorrhagic Sarcoma (Kaposi), *Am J Cancer* **26** 1-28 (Jan) 1936

8 Pautrier, L. M., and Diss, A. Kaposi's Idiopathic Sarcoma Is Not a Genuine Sarcoma but a Neurovascular Dysgenesis, *Brit J Dermat* **41**:93-105 (March) 1929

9 Jessup, D. S. D. Kaposi's Sarcoma, *Am J Cancer* **31** 556-562 (Dec) 1937

10 Aegerter, E. E., and Peale, A. R. Kaposi's Sarcoma, *Arch Path* **34**:413-422 (Aug) 1942

11 Nesbitt, S., Mark, P. F., and Zimmerman, H. M. Disseminated Visceral Idiopathic Hemorrhagic Sarcoma (Kaposi's Disease). Report of Case with Necropsy Findings, *Ann Int Med* **22** 601-605 (April) 1945

12 Sachs, W., and Gray, M. Kaposi's Sarcoma and Lymphatic Leukemia, *Arch Dermat & Syph* **51** 325-329 (May) 1945

another case, reported by Lane and Greenwood,¹³ the patient had cutaneous lesions of both Kaposi's sarcoma and mycosis fungoides and a blood picture of lymphatic leukemia

The histopathology of the disease varies in the different stages, so a microscopic diagnosis is at times difficult. MacKee and Cipollaro⁷ pointed out that inflammatory, granulomatous and neoplastic stages evolve in that order. The early lesions are largely angiomatous with new and dilated blood vessels and lymph vessels associated with edema, hemorrhage and cellular infiltration. In the later stages, the vascular sinuses become indistinct and fusiform cells proliferate, affected areas may easily be confused with the lesions of fibrosarcoma. The process in the viscera is often less angiomatous and is frequently of a pure spindle cell type.

The etiology still remains obscure. Many authors have stated the belief that the lesion is a true neoplasm, whereas others regard it as an infectious granuloma, and some consider it to be of the nature of a hamartoma derived from germ plasm. Dorfell,² after studying the histogenesis of the disease, concluded that it was a disorder of the reticuloendothelial system including a disturbance of its monocytic function which might at times terminate in true malignancy. Pautrier and Diss⁸ described structures resembling the myoneuroarterial glomus and bodies similar to Meissner corpuscles and called the disease a dysgenesis of the vessels and their neuromuscular annexes on the one side and their schwannian elements on the other. It is debatable whether visceral lesions arise in situ or represent true metastases. Of those who have done experimental work, only Justus¹⁴ reported success in animal inoculations. He claimed to have inoculated a mouse with a rapidly growing lesion and to have carried a lesion through five generations of rabbits. Becker and Thatcher¹⁵ obtained an abundant growth of spindle cells from the culture of a benign lesion, subsequent implantation under the patient's skin gave rise to a plaque of Kaposi's sarcoma, but implantation into rabbits produced negative results. Dillard and Weidman¹⁶ found myceliums and chlamydospores in the mesenteric and omental lymph nodes in a case in which the patient had disseminated lesions but did not claim the fungus to be the cause of the disease.

13 Lane, C. G., and Greenwood, A. M. Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, *Arch. Dermat. & Syph.* **27** 643-654 (April) 1933.

14 Justus, J. Über Übertragung von Sarcoma idiopathicum hæmorrhagicum Kaposi auf Tiere, *Arch. f. Dermat. u. Syph.* **99** 446, 1910, *Sarcoma idiopathicum Kaposi*, *ibid.* **151** 436, 1926.

15 Becker, S. W., and Thatcher, H. W. Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, *J. Invest. Dermat.* **1** 379-398 (Oct.) 1938.

16 Dillard, G. J., and Weidman, F. D. Multiple Hemorrhagic Sarcoma of Kaposi, *Arch. Dermat. & Syph.* **11** 203-231 (Feb.) 1925.

REVIEW OF STUDIES

The records of the Presbyterian Hospital since 1928 were searched, and reports of 13 cases of Kaposi's sarcoma were found in which the diagnosis was certain. All the patients were males, and only 2 were born in the United States. Of these 2, one was born of Russian Jewish parents. Of the remaining 11, 5 were Russian Jews, 2 were German or Austrian Jews, 3 were Italians and 1 was a Hungarian. The age of the youngest at onset was 19, and that of the oldest 74.

The table shows the decade of life in which cutaneous lesions first appeared in this group of cases. Six of the 13 patients are now dead. In 3 cases, death was attributable to Kaposi's sarcoma. The remainder of the patients died of carcinoma of the sigmoid colon, carcinoma of the bronchus or acute meningitis, so Kaposi's sarcoma was not a direct contributing cause. The duration of the disease in the 6 fatal cases ranged from two to twelve years with an average of five and a half years. For the patients still living at the time of the last observation,

Age of 13 Patients at Onset of Kaposi's Sarcoma

	Age, Years						
	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Number of patients	1	0	0	5	4	2	1

the duration ran from two to twenty years, the average was nine and a half years.

In this series of cases, pitting edema of the extremities (particularly of the legs) was a frequent finding, and in 6 cases it occurred early in the disease and either preceded or appeared shortly after the skin lesions. In 3 cases it was a late manifestation. Edema of the leg for a year was the presenting complaint of a patient in whose case considerable study and observation failed to establish a diagnosis until cutaneous lesions made their appearance. A case was also recorded in which edema of the hands and arms preceded any involvement of the skin. In another instance, there had been edema of the right leg for four or five years when a lesion on the plantar surface of the left foot was diagnosed as melanoepithelioma and a radical excision of the femoral and inguinal lymph nodes was performed. Later, a lesion appeared on the skin of the right foot, the histopathologic picture was that of Kaposi's sarcoma.

In a number of cases, evidence of the disease was found beyond the skin prior to death. Several patients showed invasion of the axillary or inguinal lymph nodes, and 1 showed lymphatic involvement of the lungs on roentgenologic examination.

Eosinophilia was not a consistent finding, but a differential count of 4 or 5 per cent eosinophils in a normal total leukocyte count was not

uncommon, occasional readings up to 17 per cent were recorded. Monocytosis, as reported by some authors, was not observed in this series.

In the case of the 1 young patient in this series who subsequently died of Kaposi's sarcoma, cultures on various mediums and inoculations of animals with tissue removed for biopsy failed to yield positive results.

It was noted that 6 (46 per cent) of the patients with Kaposi's sarcoma showed evidence of diabetes mellitus¹⁷. Three patients had frank diabetes requiring diet and insulin for control. In the mildest case 20 units of insulin daily sufficed, and in the severest case up to 60 units a day were required. Two patients showed only glycosuria (2 plus and 4 plus, respectively), but their cases were not adequately studied from the standpoint of diabetes. However, 1 of these patients gave a history of having had diabetes diagnosed six months previously and most probably had true diabetes. The remaining patient (the one in case 2 in the present report) showed glycosuria on only one occasion, but the reaction to the dextrose tolerance test was definitely diabetic in type. Two of the 6 patients had recognized diabetes prior to the diagnosis of Kaposi's sarcoma. In the remaining cases, the evidence of diabetes appeared after the cutaneous lesions.

The 2 reports illustrate the occurrence of Kaposi's sarcoma in a case of frank diabetes and in 1 of potential diabetes. Autopsy findings are included in case 1.

REPORT OF CASES

CASE 1—J. O., a Russian Jewish salesman of 49, entered Vanderbilt Clinic in September 1930, with a complaint of swelling of the right foot and leg for two years and nodular cutaneous lesions of four months' duration. He stated that several similar nodules had been "burned off" six months previously. The patient's father had died of carcinoma of the stomach, and 1 sister had mild diabetes.

The patient had been born in Russia but had lived in the United States for the past thirty-five years and, in general, had always enjoyed good health. The veins in both legs had been somewhat prominent since childhood but had caused no symptoms.

Physical Examination—Physical examination disclosed twelve firm, nontender, purplish nodules, 4 to 10 mm in diameter, on the right leg between the ankle and midcalf. Some were elevated 5 mm above the surface of the skin, and some blanched slightly on pressure. The right foot and leg were firm, edematous and cooler to the touch than the left ones. The circumference of the right leg 9 cm below the tibial tubercle was 41 cm, and that of the left leg was 38 cm. The circumference 8 cm above the medial malleolus was 30 cm on the right and 24.5 cm on the left. There was only slight varicosity of the internal saphenous veins. No lymphadenopathy was noted, and except for moderate obesity and a blood pressure of 150 systolic and 98 diastolic (later 190 systolic and 90 diastolic) the remainder of the examination gave normal results.

Microscopic Examination—Tissue was taken from one of the lesions. The report of the histologic examination, read on Nov. 19, 1930 by Dr. A. P. Stout, was as follows:

¹⁷ Dr. George C. Andrews made this observation.

"The swelling was due to a complicated growth composed of many capillaries containing blood and lined with swollen endothelial cells which were often seemingly several layers thick. The capillaries were surrounded by rather large spindle-shaped cells, arranged in bundles, which tended to interlace. The nuclei were ovoid and somewhat hyperchromatic, and mitoses averaged one to every two or three high power fields. Many of these cells were surrounded by



Fig 1—Cutaneous lesion in case 1 at a relatively early stage, showing angiomatous features. Low power field.

slender collagen fibers which were argyrophil. Other cell groups had no fibers between them. In general, when the cells were surrounded by fibers they were silver negative with Laidlaw's stain, but when they were gathered in groups they were silver positive. In some of the septums of connective tissue which separated the masses of cells and capillaries, there was blood pigment. In other places, some cells of the main tumor groups contained finely divided pigment which was blackened by the Fontana stain and which was probably melanin. About the

periphery of the main tumor mass was an advance guard of capillaries, suggesting that that was the method by which the growth extended" (figs 1 and 2)

Course—Roentgen therapy was begun, a dose of 300 r being given to different areas of the skin at varying intervals as needed to reduce the lesions. The factors used were 160 to 180 kilovolts, 4 milliamperes, 50 cm target-skin distance and a filter of 0.25 mm of copper and 1 mm of aluminum. During the ensuing years, a total of 22,200 r was given, divided among six areas on the right leg



Fig 2—Cutaneous lesion in case 1. High power field.

In November 1930, glycosuria was discovered (4 plus), the fasting blood sugar was 244 mg per hundred cubic centimeters of blood. The patient was given a diet of 185 Gm of carbohydrate, 70 Gm of protein and 60 Gm of fat, and 25 units of protamine zinc insulin was given after breakfast. Over the period of more than ten years that the patient was observed, the diabetes was fairly well controlled with essentially the same diet and insulin dosage, and new cutaneous lesions which appeared from time to time responded well to

roentgen therapy On occasion the patient was free of cutaneous lesions, but there was a brawny discoloration from treatment, and the edema of the leg persisted

During that time roentgenograms of the legs, chest and gastrointestinal tract showed a normal condition The value for total serum cholesterol was 197 mg and that for urea nitrogen 7 to 15 mg per hundred cubic centimeters The Wassermann



Fig 3—The pancreas in case 1 Low power field

reaction of the blood was negative Repeated blood counts did not give remarkable results except for occasional eosinophilia, which ranged as high as 7 per cent

On June 26, 1941, otitis media due to pneumococcus type III developed, and this was followed, on July 21, by mastoiditis, for which mastoidectomy was performed Meningitis subsequently developed, with pneumococcus type III in the spinal fluid A subdural exploration revealed no pus In spite of treatment with immune serum and sulfapyridine, the patient died on July 31

Necropsy—Necropsy revealed acute leptomeningitis, generalized arteriosclerosis with sclerosis of the coronary arteries and sclerotic scars in the kidneys, fatty degeneration of the liver and hyalinization of the islets of Langerhans. There were extensive brownish discoloration and brawny edema of the right leg, and on the skin were several hard, bluish, shotty nodules, 2 to 4 mm in diameter, but no definite internal lesions of Kaposi's sarcoma were found. Sections of the pancreas at one end showed acini together with one or two islets, around which was



Fig 4—Cutaneous lesion in case 2 at a late stage, showing mononuclear and spindle-shaped cells. Low power field.

an invasion of fibrous tissue. The acini were separated from one another by invasions of fibroblasts, and numerous capillaries and many young fibroblasts were seen. There was hyalinization of the walls of the arterioles, and a number were partially thrombosed. Some of these findings were compatible with those in cases of long-standing lesions of Kaposi's sarcoma, but in this case, in which arteriosclerosis, hypertension and diabetes were present, they were most probably the result of vascular changes (fig 3).

CASE 2—M. E., a Russian Jewish real estate salesman of 50, presented himself at the Vanderbilt Clinic in December 1937, stating that a purplish red area had developed seven years previously on the skin of the left ankle. During the next three years, dime-sized to dollar-sized purple plaques and nodules appeared on both legs, and the toes assumed a frostbitten appearance which persisted. In the three years before admission to the clinic, similar lesions had involved the trunk, arms, and face, and the patient had noticed swelling of the ankles, which was reduced after a night's rest. On occasions, he had felt slight, transient stinging sensations in the lesions but had not thought them painful.

The family history was noncontributory. The patient had been born in Minsk, Russia, and had come to the United States as a child. Except for slight exertional dyspnea during the past few years, general good health had prevailed.

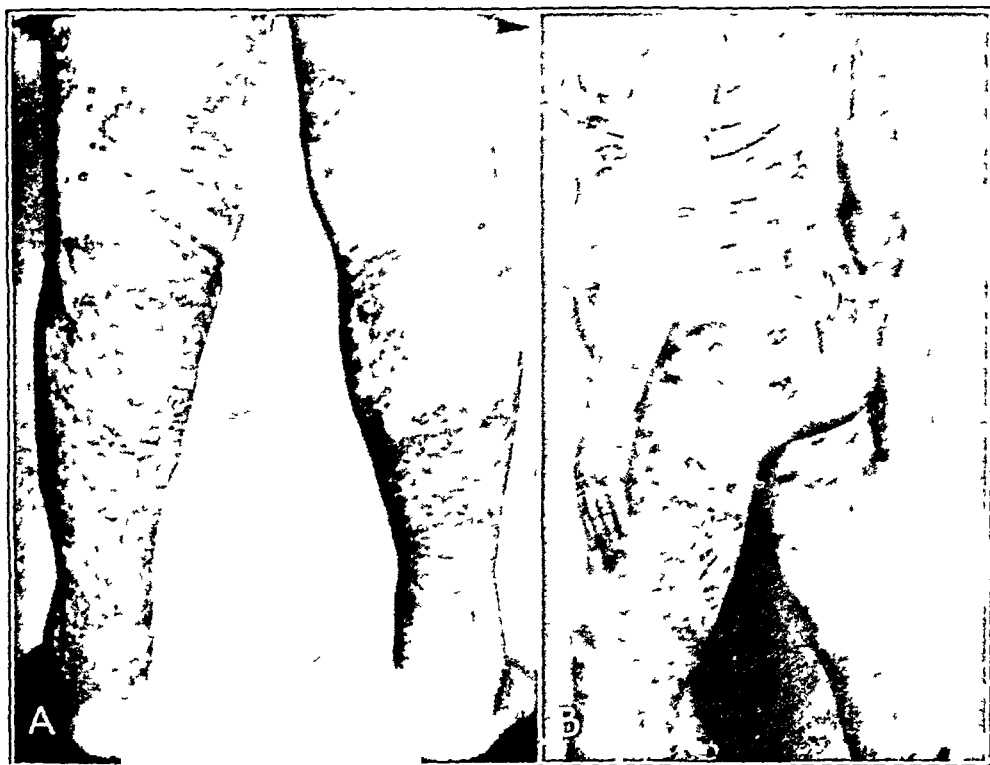


Fig 5 (case 2) —The patient, A, in September 1945, B, in January 1947

Physical Examination—Examination showed irregular, indurated plaques and nodules of a purplish color scattered over the feet, legs, hands, forearms and chest. The lesions varied in size up to 5 cm in diameter and were not tender. On the chin was a reddish macule 1 cm in diameter. Both ears were greatly thickened and of a bluish tint. The ankles and legs showed some pitting edema. Except for moderate obesity, the results of the remainder of the examination were essentially normal.

Microscopic Examination—On December 24, a biopsy was taken on a lesion on the right leg. Dr. G. F. Machacek's report was as follows:

"These sections showed a moderate hyperkeratosis with no distinct changes in the epidermis. The corium showed pronounced vascular and perivascular changes, and the walls of many vessels were thickened. About them, there was an increase of spindle-shaped cells and also a focal infiltration of mononuclear cells. Here and there, a few red blood cells were scattered through the tissue,

and there were also accumulations of coarse granules of brown pigment which were chiefly intracellular" (fig 4)

Course—The patient has been seen frequently at the Vanderbilt Clinic for almost eleven years at the time of writing, and his case has received extensive study. Roentgenograms showed the stomach and the entire skeleton normal, as were results of repeated roentgen examinations of the chest and teeth, and electrocardiograms. The basal metabolic rate was minus 7 per cent, and the Kline reaction was negative. Extensive blood chemistry studies were within normal limits, and bleeding and clotting times and platelet counts were not abnormal. Numerous blood counts did not give remarkable results except of a frequently high eosinophil count, which was once 17 per cent and on two occasions 13 per cent.

Although urinalysis and determinations of fasting blood sugar were normal, the reactions to a glucose tolerance test made in May 1941 were of the diabetic type indicated.

	Time After Administration of Glucose, Hours	Blood Sugar, Mg per 100 Cc	Urinary Reduction
Fasting		120	—
½		188	++
1		232	++++
2		208	+++
3		133	.

On June 1, the patient was admitted to the Presbyterian Hospital for six weeks for study of the effect of insulin therapy on the Kaposi sarcoma. He was given a diet of 175 Gm of carbohydrate, 80 Gm of protein and 60 Gm of fat, with insulin in gradually increasing quantities up to 50 units daily, which he tolerated well. In spite of this large amount of insulin, most determinations of blood sugar were within normal limits. The patient continued to take insulin at home until October 15, when its use was discontinued as no appreciable improvement in the cutaneous lesions could be noted.

In April 1942, a small, pedunculated tumor on the retropharynx was removed, this showed a microscopic structure of Kaposi's sarcoma. New cutaneous lesions appeared from time to time (fig 5A).

In the fall of 1946 the patient began to notice tenderness of the breasts and hot flushes, and by January 1947 there was definite mammary hypertrophy (fig 5B). A determination of the urinary 17-ketosteroids showed a normal value of 9 mg in a twenty-four hour specimen. The patient was given 25 mg of testosterone propionate intramuscularly twice a week and noted improvement of the symptoms. In September 1947, he entered the Presbyterian Hospital because of lower abdominal pain and tenderness, and a barium sulfate enema showed the presence of diverticula. There was a 1 plus degree of glycosuria. The following month the patient suffered a rupture of a diverticulum of the sigmoid colon, and a resultant peritoneal abscess was drained of 2,000 cc of purulent fluid, he made a satisfactory recovery. In August 1948, the left lacrimal duct was excised because of chronic swelling, and examination showed a structure suggestive, but not diagnostic, of Kaposi's sarcoma.

The judicious use of roentgen therapy benefited the patient more than any other form of treatment. In December 1937, the administration of 150 r twice weekly to various cutaneous lesions as needed was begun, and by July 1938 he was much improved, only pigmentation remaining at the sites of many of the lesions. However, new lesions continued to appear, some of which were described as nodular, pedunculated or lichenoid. Roentgen therapy was promptly instituted. The factors for most treatments were 135 kilovolts, 5 milliamperes, 14 to

25 cm target-skin distance and a filter of 3 mm of aluminum. Representative of the average dose was the 2,250 r given from December 1937 to December 1945 and directed to numerous individual lesions on the legs.

Other treatments given the patient at different times consisted of the administration of acetarsone (stovarsol®), vitamin K preparations, gold sodium thio-sulfate and solution of potassium arsenite (Fowler's solution). None of these medications appeared to be of appreciable benefit.

The patient had steadily maintained that sunlight caused improvement of the cutaneous lesions. In August 1948, after returning from California, where he took frequent sun baths, his skin showed considerable improvement and he appeared robust and optimistic. However, it was noted that improvement had begun about the time the feminizing changes made their appearance, and that no new cutaneous lesions had developed since. In addition to the hot flushes and the enlargement of the breasts, he had loss of libido and his usual heavy growth of body hair had become relatively sparse. He had neglected to take testosterone propionate except at irregular intervals. In October, no new lesions were present and, at the sites of a number of old lesions, the skin appeared almost normal. The ears had lost almost all induration. A few old nodular lesions on the legs appeared to be undergoing involution, and the brawny induration was somewhat decreased. Moderate edema still existed, however, particularly around the ankles.

Additional studies showed a basal metabolic rate of minus 11 per cent and 203 mg blood cholesterol per hundred cubic centimeters. A twenty-four hour urine specimen showed 21 micrograms of estrogen and 4 mg of 17-ketosteroids per hundred cubic centimeters. The value for serum chloride was normal, and a roentgenogram of the skull revealed a normal sella turcica. A glucose tolerance test showed decreased tolerance, although the reaction was not so pronounced as previously.

COMMENT

The high incidence of diabetes mellitus in this group of 13 cases of Kaposi's sarcoma appears to be more than a coincidence, and it is believed that patients with this disease should be studied with diabetes in mind. The reason for the coexistence of the two diseases is not apparent, and the cutaneous lesions of Kaposi's sarcoma do not appear to be affected by the administration of insulin. The possibility of an endocrine imbalance in cases of this condition is illustrated in case 2. Although a diagnosis of diabetes was not made in this case, the results of the glucose tolerance test and the high dosage of insulin which the patient was able to utilize suggest the presence of an abnormal anti-insulin factor. The fact that definite clinical improvement in this case began with the onset of spontaneous feminizing changes and that the disease is rare in women gives support to the rationale of treating these patients with estrogenic hormones. Although several patients in the group were treated for long periods with diethylstilbestrol without showing pronounced benefit, further study of the disease from an endocrinologic standpoint seems worth while. As far as could be determined, in the recent literature no mention has been made of diabetes mellitus associated with Kaposi's sarcoma with the exception

of the case reported by Pohle and Clark¹⁸ under the title of "Kaposi's Sarcoma or Lymphogranulomatosis Cutis" The clinical and histopathologic observations in their case would make the condition described appear to be Hodgkin's disease rather than Kaposi's sarcoma

In the presence of unexplained edema of the extremities, and especially of the legs, Kaposi's sarcoma should be considered as a possibility Almost half the patients in this series showed edema of the legs as an early symptom, and in a number of cases it appeared before any cutaneous lesions and caused the clinicians to entertain such diagnoses as filariasis or arteriovenous fistula Apparently the cause of the edema has not been extensively studied, but it would seem to arise from lymphatic obstruction, and in the later stages vascular stasis is superimposed The disease is not always easily diagnosed, even in the presence of cutaneous lesions, as evidenced by 1 case in which it was confused with melanoepithelioma The wide variation in the histologic picture of lesions in different stages of development is illustrated in the 2 cases described Roentgen therapy, although not curative, is by far the most effective form of treatment to date

SUMMARY

Thirteen cases of Kaposi's sarcoma are reviewed Six patients, or 43 per cent, either had frank diabetes or showed some evidence of that disease

Two typical cases are described in some detail, 1 with autopsy findings

One patient showed definite sustained clinical improvement following the onset of spontaneous feminizing changes

18 Pohle, E. A., and Clark, E. A. Kaposi's Sarcoma or Lymphogranulomatosis Cutis (Report of a Case Treated with Roentgen Rays), *Urol & Cutan Rev* **51** 382-385 (July) 1947

CLINICAL MANIFESTATIONS OF CARRIÓN'S DISEASE

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CARRIÓN'S disease is caused by *Bartonella bacilliformis*, a polymorphous organism classified as a bacterium in 1927 by Noguchi,¹ transmitted by sandflies of the genus *Phlebotomus*. The disease is limited geographically to certain areas of the Andean regions in Peru, Colombia and Ecuador.

The disease is extremely polymorphic in symptoms. The confusion existing in the literature arose in part from reports prior to the discovery of *B. bacilliformis*, when intercurrent infections were not recognized and many symptoms were erroneously assigned to Carrión's disease. The present report is based on a study made on several hundred cases in Lima, Peru, during the period 1938 to 1943.

HISTORY AND NOMENCLATURE

Archeologic findings indicate that the disease was known in Peru in the pre-Incaic era. Surprisingly accurate representations of the cutaneous nodules, or verrugas, are found in the Peruvian ceramic pots called *huacos*, especially in the Chinú civilization.² The first medical publication on the disease is credited to Gago de Vadilla in 1630.³

The first Spanish colonizers to arrive in Coaque, Ecuador, described a disease called *bubas* or *beirugas* which greatly resembles Carrión's disease.⁴ Apparently in the Keshua language used by the Indians, the

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The clinical observations were carried out at the Hospitals "Dos de Mayo," Arzobispo Loayza, San Bartolome, Maternidad, and "del Niño" in Lima, Peru.

1 Noguchi, H. The Etiology of Verruga Peruana, *J. Exper. Med.* **45** 175, 1927.

2 La céramique péruvienne de la société d'études Américaines, congress international des Américanistes, *Compt. rend. d. trois Sess. Brux.* **1** 470, 1879. Lastres, J. B. La semiología en el Perú, *Rev. méd. peruana* **7** 421, 1935.

3 Valdizán, H. Apuntes para la historia de la verruga peruana, *An. Fac. med., Lima*, numero extraordinario, 1925, p. 34, Apuntes para una bibliografía peruana de la enfermedad de Carrion, *ibid.*, 1925, p. 45.

4 Rebagliati, R. Verruga peruana (enfermedad de Carrión), Lima, Imprenta Torres Aguirre, 1940.

presence of verrugas was known as *Kceppo*⁵ and *Sirki*⁶. Because of the characteristic presence of nodules in the skin, Bueno⁷ in 1764 referred to it as the disease of *berugas*. Tschudi,⁸ in 1845 called the lesions "blood verrugas" because of the marked vascularity of the nodules, they are also called "warts of the Andes"⁹ because of the prevalence of the disease in these mountains. As the disease was first thought to exist only in Peru, it had the name *verruca peruana* (*verruca peruviana*).

All data referred to the cutaneous manifestations, the verrugas, until 1870, when during the building of the Central Railway from Lima to Oroya, in many of the workers a severe anemia and fever developed, the nature of which was unknown. This disease, which produced a mortality of nearly 7,000, was given the name of Oroya fever. This is a misnomer, since the disease does not exist in the Peruvian city of Oroya. Espinal, a Peruvian clinician, in his unpublished clinical lectures, made an accurate observation of the course of the anemic patients and noted that in some verrugas later developed in the skin. He suggested that the two features were probably manifestations of the same disease. In 1885, Daniel A. Carrion, a medical student at the University of San Marcos in Lima, Peru, sacrificed his life to show the relation of Oroya fever to *verruca peruana*. He was inoculated by a classmate with the blood from one of the verrugas of a patient. Twenty-one days later a very marked anemia, fever and other manifestations of Oroya fever convinced the attending physicians of Lima that the two conditions were merely different phases of the same disease.¹⁰ Numerous clinical studies followed, and in 1898 Odriozola published an excellent and complete monograph on the disease.¹¹

In 1909, Alberto Barton, another Peruvian physician, described with great accuracy the pathogenic organisms in the circulating erythro-

5 Vargas-Fano, J. A. La verruga peruana a travez de la historia, Thesis, Lima, 1938.

6 Matto, D. Discurso, Cron. med., Lima 3 377, 1886.

7 Bueno, C., Cited by Rebagliati.⁴

8 (a) von Tschudi, J. J. Die Verrugas, Arch. f. physiol. Heilk. 4 378, 1845.
(b) Ueber die geographische Verbreitung der Krankheiten in Peru. Mitgetheilt von Dr. Endlicker, Oesterr. med. Wchnschr., 1846, pp. 373, 407, 437, 467, 507, 537, 595, 627, 656, 661, 694 and 725. (c) Tupper.²¹

9 Bordier, A. La geographie medicale, Paris, C. Reinwald, 1884. Salazar, T. Historia de las verrugas, Thesis, Lima, 1858.

10 (a) Medina, C., Mestanza, E., Arce, J., Alcedan, M., and Miranda, R. La verruga peruana y Daniel A. Carrion, Lima, 1886, An. Fac. med., numero extraordinario, 1925. (b) Alcedan, M. Enfermedad de Carrion, Cron. med., Lima 3 381, 1886.

11 Odriozola, E. La maladie de Carrion, ou la verruga peruvienne, Paris, G. Carre & C. Naud, 1898.

cytes¹² Skepticism in accepting this organism as the causative factor in the disease was due primarily to the fact that other bacteria, reported earlier by the same author as the pathogenic organisms,¹³ were later demonstrated to be due to an intercurrent paratyphoid infection¹⁴

Jadassohn and Seiffert¹⁵ in 1910 proved the infectious nature of the verrugas by transmitting the disease in monkeys, their studies were later confirmed¹⁶ A dual concept of the disease was described by Strong¹⁷ and associates in 1913 These authors recognized *B bacilliformis* as the pathogenic agent of Oroya fever but not of the verrugas, which they supposed represented a different disease altogether In 1925 Noguchi and Battistini¹⁸ were able to culture *B bacilliformis* A year later the same authors¹⁹ were able to culture the bartonella organisms from the verrugas of monkeys, thus proving Espinal's unitary concept of the disease

The term "malignant" has been applied with different meanings in Carrión's disease to the fatal cases with verrugas,⁷ to the fatal anemic forms¹¹ and also to particular cases in all different stages of the disease²⁰ The terms "benign" and "malignant" still used in Carrión's disease should be discarded, since they have been used for different purposes by various authors and are meaningless

CLINICAL COURSE

In Carrión's disease there are several stages—incubative, invasive, preeruptive and eruptive

12 Barton, A L Descripción de elementos endo-globulares hallados en los enfermos de fiebre verrucosa, *Crón méd*, Lima **26** 7, 1909

13 Barton, A L El germen patógeno de la enfermedad de Carrion, *Crón méd*, Lima **18** 193 and 310, 1901, **19** 348, 1902

14 Tamayo, M O Apuntes sobre la bacteriología de la enfermedad de Carrion, *Cron méd Lima* **22** 335, 1905

15 Jadassohn, and Seiffert, G Ein Fall von Verruga peruviana Gelungene Uebertragung auf Affen, *Ztschr f Hyg u Infektionskrankh* **66** 247, 1910

16 (a) Mayer, M, Rocha-Lima, H, and Werner, H Investigaciones sobre la verruga peruana *Crón med*, Lima **30** 193, 1913 (b) da Rocha, H Zur Histologie der Verruga peruviana, *Verhandl d deutsch path Gessellsch* **16** 409, 1913

17 Strong, R P Report of the First Expedition to South America, Cambridge, Mass, Harvard University Press, 1913

18 Noguchi, H, and Battistini, T Etiology of Oroya Fever II Cultivation of Bartonella Bacilliformis, *J Exper Med* **43** 851, 1926

19 Noguchi, H Etiology of Oroya Fever II The Viability of Bartonella Bacilliformis in Cultures and in the Preserved Blood and an Excised Nodule of Macacus Rhesus, *J Exper Med* **44** 533, 1926, Etiology of Oroya Fever III The Behavior of Bartonella Bacilliformis in Macacus Rhesus, *ibid* **44** 697, 1926, IV The Effect of Innoculation of Anthropoid Apes with Bartonella Bacilliformis, *ibid* **44** 715, 1926

20 Arce, J Apuntes sobre la enfermedad de Carrión, *Crón méd*, Lima **30** 325, 1913

1 *Incubation Period*—The length of the incubation period has been subject to much controversy Tupper²¹ in 1877 reported a fluctuation of few days to several months, whereas Carrión^{10b} considered that it lasted from eight to forty days The first experimental human observation, made by Carrión on himself in 1885, indicated a twenty-one day incubation before the appearance of the acute febrile anemia which led to his death^{10b} Prior to this, the beginning of the eruption of the verrugas, or what is today called the preeruptive stage, was mistaken as the incubation period Antunez²² reported seven to twenty-one days as the incubation period, Arce,²³ from twelve to forty days, and Odrizola,¹¹ fifteen to forty days The last-named author denied that the incubation could be of many months' duration, an opinion shared by other authors²⁴ An accidental inoculation was followed by onset of the disease twenty days later,⁴ Kuczinski²⁵ made a second experimental self inoculation, the initial symptoms appearing seventeen days later Mackehenie²⁶ showed that marked variability can occur, as he observed cases without any symptoms suggesting the disease but with blood cultures positive for *B bacilliformis* In a previous study of 13 cases²⁷ when blood specimens were cultured for *B bacilliformis* on Geiman medium,²⁸ I found that the period of incubation varied from nineteen to one hundred days

The difficulties in determining the duration of the incubation period were based primarily on the very limited number of observations and of the lack of reliability of the patients' histories The disease frequently has a variable symptomatology and occasionally is without symptoms during its entire course, making it very difficult or impossible to diagnose without blood cultures Battistini,²⁹ Weinman,³⁰ Weinman and Pinker-

21 Tupper, F P Ueber die Verruca peruviana, Berlin, g Schode, 1877, Rev med de Chile, pp 271, 293, 330 and 353 1878-1879

22 Antunez, D Enfermedad de Carrion, Cron med, Lima 7 290, 1890

23 Arce, J Verrue peruvienne ou maladie de Carrion, Rev Sud-am de med et de chir 2 1017, 1931

24 Castillo, J C Verruga peruana, Crón med, Lima 11 259, 275, 289 and 305, 1894

25 Kuczinski, G M La inmunidad fisiológica, Reforma med 23 277, 313, 609 and 648, 1937

26 Mackehenie, D La verruga peruana y la familia tifo-exantematica, An Fac med, Lima 18 245, 1935

27 Ricketts, W E Carrion's Disease A study of the Incubation Period in Thirteen Cases, Am J Trop Med 27 657, 1947

28 Geiman, Q New Media for the Growth of Bartonella Bacilliformis, Proc Soc Exper Biol & Med 47 329, 1941

29 Battistini, T, Estudio sobre la verruga peruana, Bol dir salub pub Lima, 1927, p 191

30 Weinman, D Reservoirs of Bartonella Bacilliformis and Asymptomatic Human Bartonellosis, Proc Pacific Sc Cong 5 781, 1939

ton³¹ and Hurtado³² have demonstrated that persons without symptoms may have the disease. Atypical symptoms during the invasive stage include headache, pain in the bones and joints and moderate fever lasting for a few days. In many cases, such vague and indefinite symptoms are incorrectly interpreted as "flu," "gastrointestinal upsets," etc.³³

2 Invasive Stage—The features of the invasion vary with respect to symptoms, duration and prognosis, however, clinically, the predominant symptoms are fever and anemia, although they may sometimes be absent. The onset of the disease, as described in a previous paper,³³ may develop insidiously with anorexia, slight fever, headache, malaise, frequently lasting from two days to one week or longer, or it may start suddenly with chills, high fever, copious sweating, headaches and occasionally delirium. The chills never exhibit the definite periodicity typical of malaria. It is important to separate the cases without and with *B. bacilliformis* anemia in the invasive stage.³⁴ (a) In cases without anemia there are nonspecific symptoms, such as malaise, headache and occasional fever, in these cases diagnosis cannot be made at this stage of the disease unless blood cultures are secured. (b) *B. bacilliformis* anemia (synonyms: Oroya fever, fiebre grave de Carrion,¹¹ fiebre verrucosa de Guaitara³⁵) is a febrile hemolytic anemia with bartonella organisms parasitizing the erythrocytes. It occurs infrequently during the invasive stage of Carrion's disease. It is interesting that in areas where the disease is endemic, the anemia is infrequent. At present, however, there is no statistical report available from these endemic areas indicating the exact incidence of *B. bacilliformis* anemia in Carrion's disease.

B. bacilliformis anemia has distinguishing clinical and hematologic features and develops so rapidly that it can be compared only with the

31 Weinman, D., and Pinkerton, H. Carrion's Disease. IV. Natural Sources of Bartonella in the Endemic Zone, *Proc Soc Exper Biol & Med* **37** 596-598, 1937.

32 Hurtado, A. "Daniel A. Carrion," Report of an Address, *Bol informat Asoc med Peruana* **6** 261, 1939.

33 Ricketts, G. Contribucion al estudio clinico de la enfermedad de Carrion, Thesis, Lima, 1942.

34 Ricketts, W. E. Bartonella Bacilliformis Anemia (Oroya Fever). A Study of Thirty Cases, *Blood* **3** 1025, 1948.

35 (a) Patino Carmargo, L. Bartonellosis en Colombia. Bartonellosis de Guaitara o fiebre verrucosa del Guaitara, *Rev Fac de med*, Bogota **7** 467, 1939, (b) Un nouveau foyer de bartonellose en Amerique. *Bull Office internat de'hyg pub* **32** 570, 1940 (c) Patiño Carmargo, L., Cifuentes, P., and Sanchez Herrera, M. El primer caso de bartonellosis (fiebre verrucosa del Guaitara o verruga) en Bogota, *Bol ofic san panam* **19** 1070, 1940 (d) Patiño Carmargo, L. Estado actual de la bartonellosis (fiebre verrucosa, verruga) en el continente americano, *Rev Fac de med*, Bogotá **9** 160, 1940.

anemia occurring in an acute hemorrhage. This anemia occurs irrespective of age, sex or race.

The physical findings in the patients with severe anemia are rather dramatic and almost pathognomonic. The patients are deeply apathetic and have a peculiar discoloration of the skin and scleras due to the combination of slight icterus with very severe anemia. The conjunctivas and the matrixes of the nails are almost colorless and the ears almost transparent. The cardiovascular signs consist in tachycardia and soft hemic murmurs of varied intensity heard over the entire precordium, synchronously there are suprasternal, epigastric and carotid pulsations, the blood pressure is moderately hypotensive, and occasionally there is peripheral collapse. In contrast to previous reports, dyspnea at rest is very unusual in anemic patients without intercurrent infection,³⁶ even with erythrocyte counts below 1,000,000, in patients with some intercurrent infection, especially with salmonellosis, it is a constant finding.³⁷ Cough and expectoration with rhonchi and rales on physical examination early in the disease may simulate a primary infection of the upper respiratory tract. Headache, vertigo, restlessness and drowsiness, tinnitus, insomnia and occasionally angina pectoris are symptoms dependent on the intensity of the anemia. Patients often complain of a feeling of transmission of the cardiac impulse to the head and ears. Odriozola said, "The patient hears his murmurs."

Thirst and anorexia are common features. The tongue is usually dry with a coffee-brown coating. In the early stages of the anemia profuse sweating may occur, but later the skin becomes very dry, a significant point in the differentiation from malaria. There is a generalized lymphadenopathy with nontender lymph nodes of the size of a small bean without periadenitis. Enlarged lymph nodes occurred in all except 3 fatal cases. Enlargement of the spleen, which had been described as a constant finding,³⁸ appeared only in the cases with intercurrent infections in this series, thus confirming a previous report.³⁹

Observations on the course and type of fever in the past have been varied and even contradictory.⁴⁰ Ordinarily after a variable onset with or without chills, the temperature fluctuates between 37.5 and 38.5

36 Hurtado, A., Pons, J., and Merino, C. La anemia en la enfermedad de Carrion o verruga peruana, *An. Fac. med., Lima* **21** 25, 1938. Odriozola.¹¹

37 (a) Ricketts, W. E. Intercurrent Infection of Carrion's Disease. *Am. J. Trop. Med.* **28** 437, 1948. (b) Odriozola.¹¹ (c) Barton.¹³

38 Odriozola.¹¹ Tamayo.¹⁴ Castillo.²⁴

39 Arce, J. Apreciaciones generales sobre el diagnostico y la clinica. La verruga peruana no genera esplenomegalia, *An. Fac. med., Lima* **7** 5, 1921.

40 (a) Mimbella, P. S. La curva térmica de la enfermedad de Carrion, *Cron. med., Lima* **14** 357, 1897. (b) Larrea y Quezada, A. Contribución al estudio de la verruga peruana, *ibid.* **4** 391, 1887. (c) Odriozola.¹¹ (d) Tamayo.¹⁴ (e) Antunez.²² (f) Castillo.²⁴ (g) Arce.²³

degrees C (99.5 and 101.3 F), but it may be higher or lower, and occasionally patients with severe anemia have an almost afebrile course. The severity of the anemia does not parallel the intensity of the fever, intermittent fever being due to concurrent malaria.^{37a} Odriozola¹¹ observed that in many cases there was later a pronounced elevation of temperature, which he interpreted as prodromal to a second outbreak, or "hyperthermic" course. This elevation of temperature has been found^{37a} to be associated with intercurrent infection, usually due to *Salmonella* organisms.

The hemorrhagic tendency may be manifested by petechiae, ecchymoses, epistaxis, gingival hemorrhage, hematemesis or melena. Petechial hemorrhages were mentioned in the first descriptions of the disease⁴¹ and occurred in the martyr Carrion.^{10a} Pinpoint hemorrhages were originally thought to be produced by the beginning eruption of verrugas¹¹ and the epistaxis supposedly produced by verrugas in the mucosa of the nose. This explanation was not satisfactory, for in most of the cases with epistaxis the bleeding occurred during the initial stage of the disease, when verrugas were not seen. Malo⁴² first made this differentiation between the petechiae and the pinpoint verrugas in the skin. I⁴³ demonstrated in previous studies that in cases with purpura there is a constant thrombopenia.

Clouding of the sensorium and delirium are rather common.⁴⁴ In most anemic cases mental symptoms, such as irritability and insomnia, were of secondary importance, however, in other cases the mental symptoms constituted a real psychosis. Pierola⁴⁵ first described these psychotic episodes and considered them transitory and related to the course of the disease. Alterations of the memory and consciousness were found in a previous study³³ of 30 patients with *B. bacilliformis* anemia. 8 of whom had meningoencephalitic symptoms.³⁴

As early as 1898, Tamayo⁴⁶ and Hercelles⁴⁷ described a fall in the erythrocyte count and in the hemoglobin values together with anisocytosis.

41 (a) Barton, A. La enfermedad de Carrion y las infecciones simitificas. Su diferenciación, *Crón. med.*, Lima **31** 37, 1914. (b) Manrique, E. El problema terapeutico de la fiebre anemizante grave de Carrion, *Reforma méd.*, Lima **23** 681, 683 and 694, 1937. (c) Landauro, A. Complicaciones de los enfermos de verruga peruana, *Crón. med.*, Lima **54** 46, 1937. Odriozola¹¹

42 Malo, N. Verruga peruana. Thesis, Santiago, 1852, *Crón. med.*, Lima **23** 295, 1906.

43 Footnotes 33 and 34.

44 Valdizan, H. El delirio de la enfermedad de Carrion, *Crón. med.*, Lima **36** 263, 1919. Ricketts³³

45 Pierola, L. O. Vesania verrucosa, *Crón. méd.*, Lima **20** 305, 1903.

46 Tamayo, M. O. Hematología de la enfermedad de Carrion, *Crón. med.*, Lima **15** 337, 1898.

47 Hercelles, O. Ligeros apuntes sobre la histologia patológica de la verruga peruana, *Crón. méd.*, Lima **17** 353 and 369, 1900, **18** 3 and 17, 1901.

tosis and poikilocytosis. Since then, many hematologic studies have been made in *B. bacilliformis* anemia,⁴⁸ including a very complete monograph by Hurtado, Pons and Merino.³⁰ The anemia is macrocytic and usually hypochromic, and the erythrocyte count may drop as low as 500,000 in the first two to four weeks of illness. The hematocrit reading decreases proportionally to the fall in the erythrocytes. The peripheral blood shows marked regenerative activity of both erythroid and myeloid series, and the number of nucleated red cells may be exceedingly high. In a previous paper³¹ a case was reported in which there were 20 erythroblasts and 461 normoblasts to each 100 leukocytes, or 37,164 normoblasts per cubic millimeter. Frequently refractile basophil granulations, nuclear particles, Howell-Jolly bodies, polychromasia, poikilocytosis and anisocytosis are found in the erythrocytes. Reticulocytes may increase to 50 per cent.

The pathognomonic sign of the disease in the erythrocyte is the organism *B. bacilliformis*. This organism is very polymorphic. In Giemsa staining it appears as though red-violet rods are situated on the red cells, and the "bacilliform" bodies may be as numerous as 20 on each erythrocyte in heavy infections (fig. 1). The length of the organism varies from 1 to 3 microns and the width from 0.25 to 0.50 micron. They are distributed in rods in a Y, V or chain appearance and they may be curved or show polar enlargement.¹⁷ These organisms are well stained by the May-Grunwald-Giemsa method or by any of the modifications of the Romanowski method. As to the relation of the bartonellas to the red cells, which has been a controversial point, modern studies⁴⁹

(48) (a) Arce, J. La anemia de la fiebre grave de Carrión, Estudio comparado con otras anemias, Su mecanismo, *Actas y trab. d. V Cong. lat. am. med.* **5** 22, 1914. (b) Napanga, J. El hemograma de Schilling en la enfermedad de Carrión, Thesis, Lima, 1938. (c) Gastriaburu, J. C., and Rebagliati, R. Sobre la hematología. La etiología de la enfermedad de Carrión, *Crón. méd.*, Lima **26** 377, 1909. (d) Barton, A. Descripción de elementos endo-globulares hallados en los enfermos de fiebre verrucosa, *ibid.* **26** 7, 1909. (e) Monge, C. Algunos apuntes sobre la hematología de la "enfermedad de Carrion," Thesis, Lima, 1910, *ibid.* **27** 297, 317 and 326, 1910. (f) Rebagliati, R. Los cuerpos de Barton, *ibid.* **32** 36, 1915, *Reforma med.*, Lima **1** 5, 1915. (g) Weiss, P. Contribución al estudio de la verruga peruana o enfermedad de Carrion, *Rev. med. latino-am.* **18** 1121, 1933. (h) Carvallo, J. La médula ósea en la enfermedad de Carrión, Thesis, Lima, 1910, *Crón. méd.*, Lima **28** 34, 42, 57, 78, 85, 110, 120 and 135, 1911. (i) Hercelles, O. Hematología de la enfermedad de Carrion, *Actas y trab. d. V Cong. lat. am. Med.* **2** 28-49, 1914. (j) Monge, C., and Weiss, P. Sobre la hematología de la enfermedad de Carrión, *An. Fac. med.*, Lima, 1927, *Rev. sud-am. de med. et de chir.* **1** 570, 1930. (k) Tamayo, M. O. Fisiología morbosa de los órganos hematopoyéticos en la enfermedad de Carrión, *Crón. med.*, Lima **16** 431, 1899. (l) Gastriaburu, J. C., and Rebagliati, R. Sobre la hematología y la etiología de la enfermedad de Carrión, *ibid.* **26** 377, 1903.

49 Aldana, L. G. La bacteriología de la enfermedad de Carrión, *Rev. méd. peruana* **46** 235, 1929.

tend to indicate that the bartonellas are not located within the red cells but are, rather, superimposed on them

While leukocytosis has been described in this anemia,⁵⁰ a normal leukocytic count³⁶ or even a tendency toward leukopenia⁴⁸¹ has also been

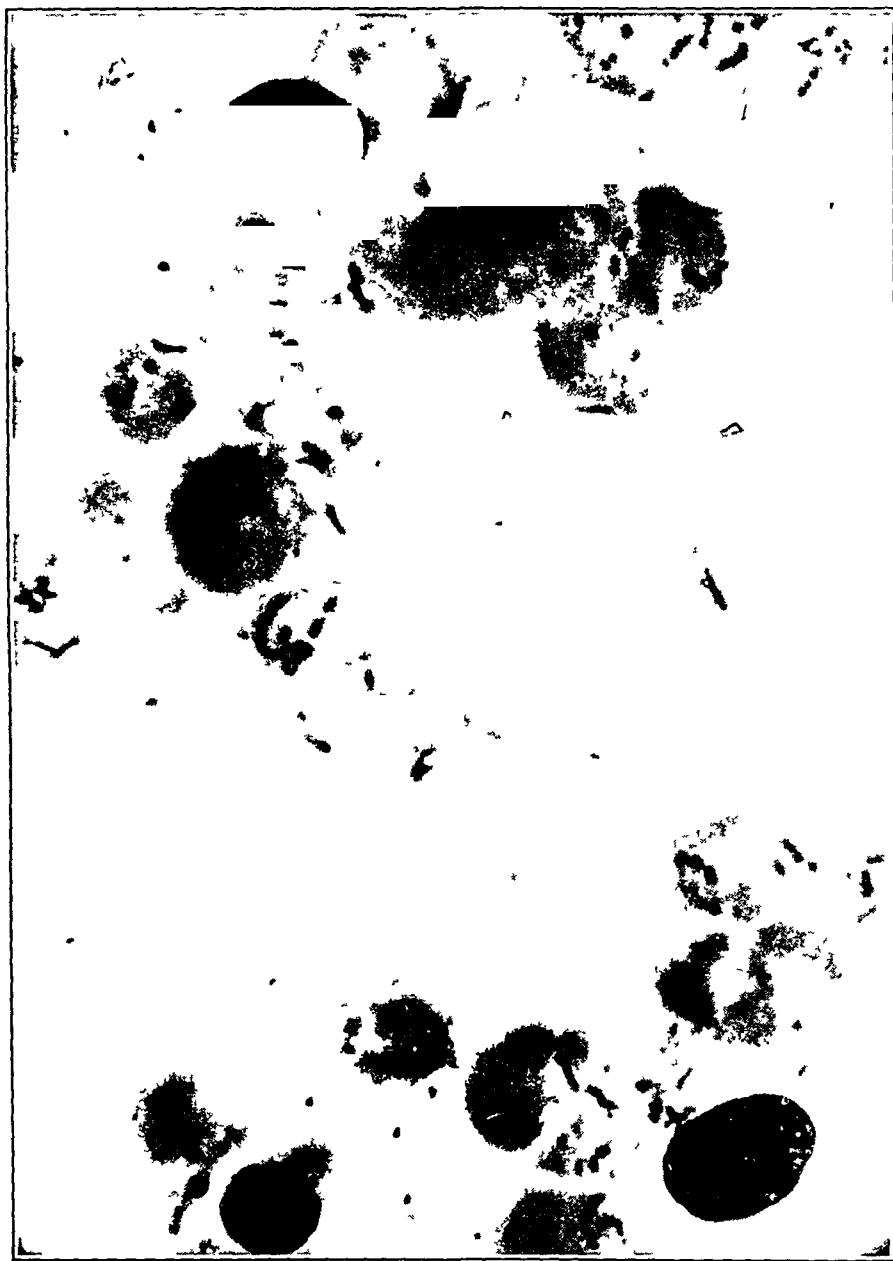


Fig 1—Massive parasitism of erythrocytes in the peripheral blood by *B bacilliformis*. Bartonellas are present on the cells and outside the cells. Giemsa stain, $\times 2,200$

reported. In a previous study it was reported³⁴ that the leukocyte count varies in each case and in the same patient during the course of the

⁵⁰ Weiss, P. Hacia una concepción de la verruga peruana, Thesis, 1927, An Fac de med, Lima 9 279, 1926. Larrea y Quezada^{40b} Monge and Weiss⁴⁸¹ Gastiaturu⁴⁸¹

disease Slight leukocytosis is not uncommon, but marked leukocytosis in cases without intercurrent infections is extremely rare A very frequent finding is a shift to the left characterized by the presence of myeloblasts, myelocytes and metamyelocytes The leukocyte count appears to be of value as an index to the course of the bartonella infection and in detecting intercurrent infections

Thrombopenia has been found³³ in 8 cases with purpura and external hemorrhages These hemorrhages were transitory and lasted no more than two weeks, being parallel to the drop in the platelet count

The interaction between the bartonellas and the reticuloendothelial system has been studied extensively⁵¹ The bartonellas are found in large numbers in the phagocytic cells, such as the Kupffer cells of the liver, littoral cells of the spleen, and in the lymph nodes, indicating clearly that the activity of the bartonellas is centered in the reticuloendothelial system

The term "critical stage"^{18c} in B bartonella anemia is applied to the period of transition in which the organism suddenly disappears from the red cells³⁴ The mechanism of this change is not entirely understood, but within a few days the bartonellas may disappear from the peripheral erythrocytes The hematologic signs of this transition are as follows (a) a change in the form of the bartonellas from a bacilliiform to a coccoid, originally described by Barton¹² as blurring of the outline of the organism with the appearance of sphere, hourglass, pear shape or granule forms (these are the coccoid bartonellas), (b) a decrease in the number of parasitized erythrocytes and in the number of bartonellas on each erythrocyte, (c) an increase in the erythrocyte count (fig 2), (d) a return to normal from the indirect hyperbilirubinemia, (e) an increase in the number of reticulocytes, (f) a decrease in the macrocytosis, the erythrocytes later in the disease regaining normal size, even having a tendency to microcytosis (g) lymphocytosis and the reappearance of monocytes and eosinophils, and (h) in the leukocytes a shift of the polymorphonuclear series to the "right," a characteristic which persists during the rest of the disease Clinically, corresponding with this transition, the fever disappears, the subicteric tinge of the skin and scleras disappears leaving an intense earthen gray pallor With the

51 (a) Noguchi, H The Etiology of Oroya Fever Pathological Changes in Animals Experimentally Infected with Bartonella Bacilliiformis, Distribution of the Parasites in Tissues, J Exper Med **45** 437, 1927 (b) Pinkerton, H, and Weinman, D Carrion's Disease Comparative Morphology of the Etiological Agent in Oroya Fever and Verruga Peruviana, Proc Soc Exper Biol & Med **37** 591, 1937, (c) Carrion's Disease Behavior of the Etiological Agent Within Cells Growing or Surviving in Vitro, *ibid* **37** 587, 1937 (d) Alzamora-Castro V Enfermedad de Carrion Un ensayo sobre patogenia, An Fac med, Lima **23** 9, 1940 (e) Mackehemie, D Mesenquime et maladie de Carrion, Rev sud-am de méd et de chir **3** 326, 1932 (f) Footnote 26

prompt rise in the number of erythrocytes, the symptoms of anemia, such as fainting, dizziness, tinnitus, etc., as well as the hemic heart murmurs, disappear, the blood pressure rises and the patient appears to be convalescing. However, this sequence of events does not always occur, for clinical improvement does not always parallel the disappearance of *B*

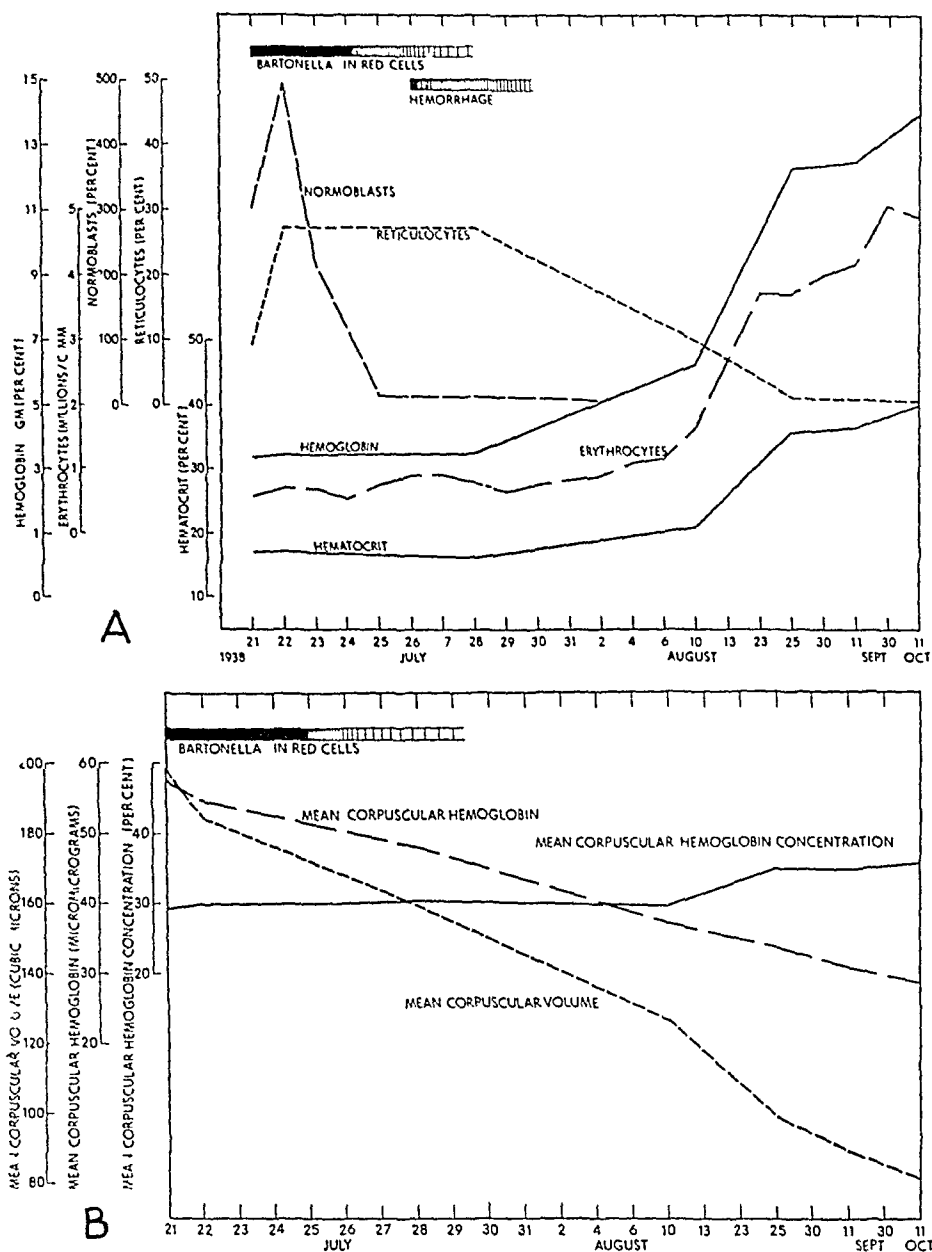


Fig 2—Recovery phase in a case of *B. bacilliformis* anemia. *A*, parallel increase of erythrocytes, hemoglobin and hematocrit values, *B*, mean corpuscular values, showing the striking fall in the mean corpuscular volume. The solid bar indicates a heavy concentration of *B. bacilliformis*, the progressively lighter shading indicates progressively diminishing numbers of parasites.

bacilliformis from the erythrocytes. There may be an increased severity of the clinical course of the disease, which is due to an atypical course of the disease itself or to the onset of intercurrent infections. It is not

known whether the bartonella infection itself is responsible for death in these cases

Intercurrent infections may develop in these patients during the critical period of the anemia, when there appears to be a lowered resistance of the host to invading organisms harbored in the gastrointestinal tract³⁷ These organisms frequently produce a fatal septicemia In these cases the symptoms are bizarre and confusing There is usually a rise in the temperature, tachycardia, diarrhea, dyspnea and psychomotor excitability, followed shortly by death There is leukocytosis with shift to the left in the polymorphonuclear series and a fall in the number of reticulocytes and normoblasts Blood cultures and examination of blood smears for malaria parasites are very helpful in determining the complicating organism

B bacilliformis anemia is a hemolytic anemia in which the destruction of erythrocytes is due to B bacilliformis The rate of destruction of the erythrocytes and the increased bilirubinemia³⁸ are directly proportional to the number of parasitized erythrocytes Hurtado, Pons and Merino³⁹ have shown that the fragility of the erythrocytes is normal in this disease There are no spherocytes, and hemoglobinuria does not occur Enlargement of the spleen is not demonstrable on physical examination in cases without intercurrent infections⁵²

An early suggestion was that the B b a was "addisonian" anemia Guzmán Barrón⁵³ demonstrated the presence of Castle's principle in the gastric secretion, and careful hematologic studies³⁶ have shown that the anemia is normoblastic and not megaloblastic and is accompanied by marked reticulocytosis Histologically there is evidence of destruction of erythrocytes in the reticuloendothelial system, as the Kupffer cells, littoral cells of the spleen and lymph nodes and other phagocytes appear filled with bartonellas and erythrocytes (fig 3)

3 *Preeruptive Stage*—This stage, between the febrile anemia of the invasive stage and the eruption of verrugas, Odriozola¹¹ called "intermediate" and Weiss "preeruptive"⁵⁴ Many interesting clinical forms, such as phlebitis, pleuritis and encephalitis, occur chronologically between the invasive and eruptive stages but are unrelated to the anemia or to the eruption of verrugas

This stage is usually not accompanied with fever, except when manifestations of the disease such as phlebitis and erythema⁵⁵ produce it

52 Ricketts³⁴ Mimbella^{40a}

53 Guzman Barrón, A La reaccion de Van den Bergh, hemoaglutininas y hemolisis en la enfermedad de Carrion, Cron med, Lima 43 79, 1926

54 Weiss, P Contribucion al estudio de la verruga peruana o enfermedad de Carrion, Rev med latino-am 18 1121, 1933 Footnote 48

55 Ricketts, R, and de Guillermo, C Reaccion de tipo eritematoide en el periodo pre-eruptivo en un caso de enfermedad de Carrion, Rev estud med, Lima 3 7, 1939

Pain is one of the most constant and most frequent symptoms of the preeruptive stage. The pains are located in the bones, joints and muscles. When in the bones and joints, they are particularly in the forearms, wrists, feet, heels, elbow, shoulders and in the epiphyses of the long bones. The pains are transitory, lasting from a few minutes

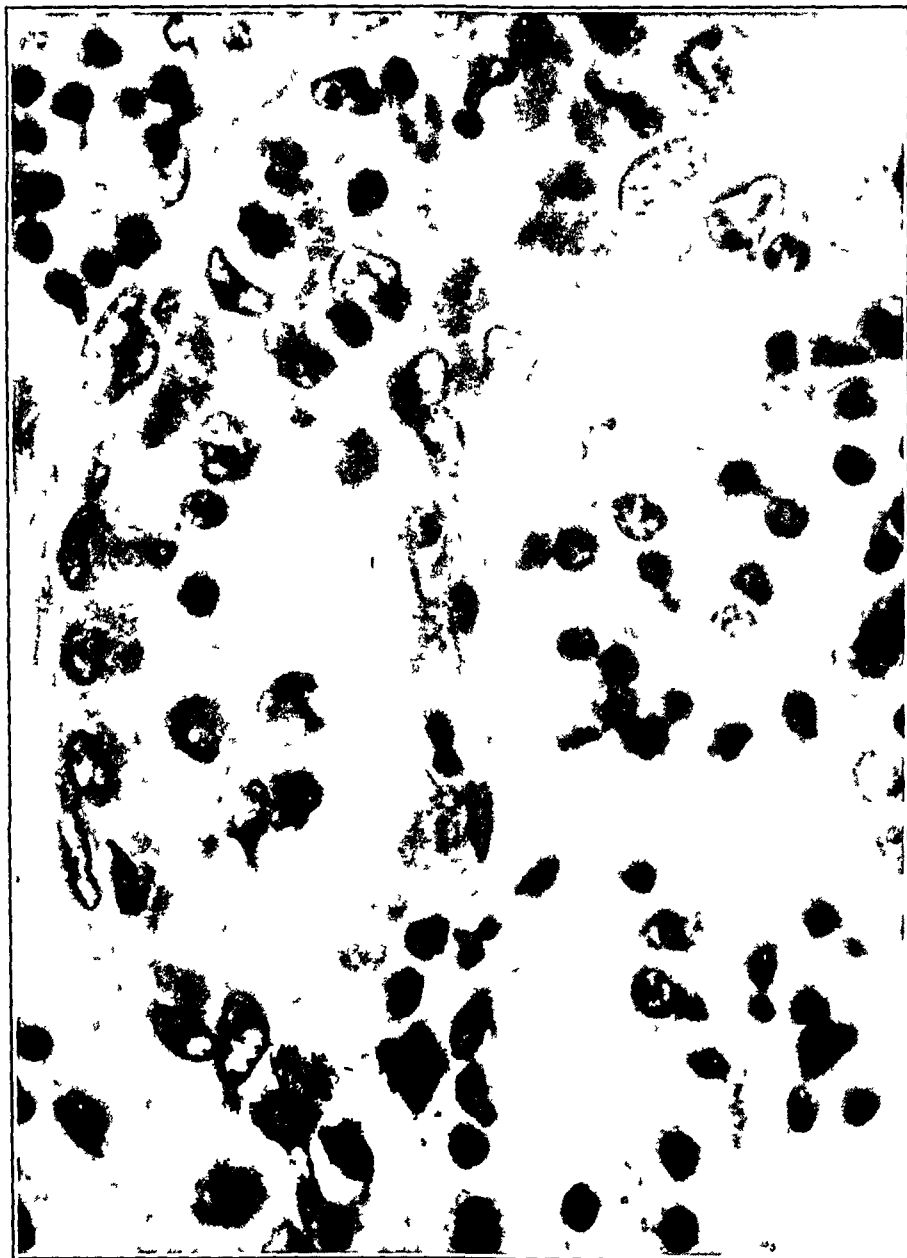


Fig 3—Large littoral cells lining the splenic sinus, with colony-like masses, each composed of innumerable bartonellas. Giemsa stain

to two or three days, and the patients say they “jump” from one bone or group of bones to another. They can be very severe and are often accentuated at night or on exposure to cold but are rarely influenced by external pressure. Pains in joints can be very annoying, occurring with

slight or no local evidence of inflammation. The pain in the muscles is transitory and changeable, appearing most frequently in the muscles of the back of the neck, deltoid, gastrocnemius and sternocleidomastoid muscles,³³ but it is rarely of marked intensity. The pains do not respond to salicylates. Cramps are not infrequent.



Fig 4—*A*, nodular facial verrugas with blood oozing from the lesion over the right eyebrow. *B*, multiple verrugas of varying sizes on the left upper extremities spreading over the extensor surfaces of the hands and arms. *C*, multiple confluent small verrugas on the dorsa of the hands. *D*, similar lesions about the elbows.

Cases with pains in the bones, joints, tendons, or muscles were described in the last century as “rheumatoid types” of the disease.⁵⁶

⁵⁶ Medina and others¹⁰⁷; Odriozola.¹¹

There are instances in which the differential diagnosis has challenged the diagnostic acumen of the best clinicians, being mislabeled as "rheumatic disease," "brucellosis" or other similar conditions, until the appearance of verrugas led to the correct diagnosis Kuczinsky²⁵ inter-

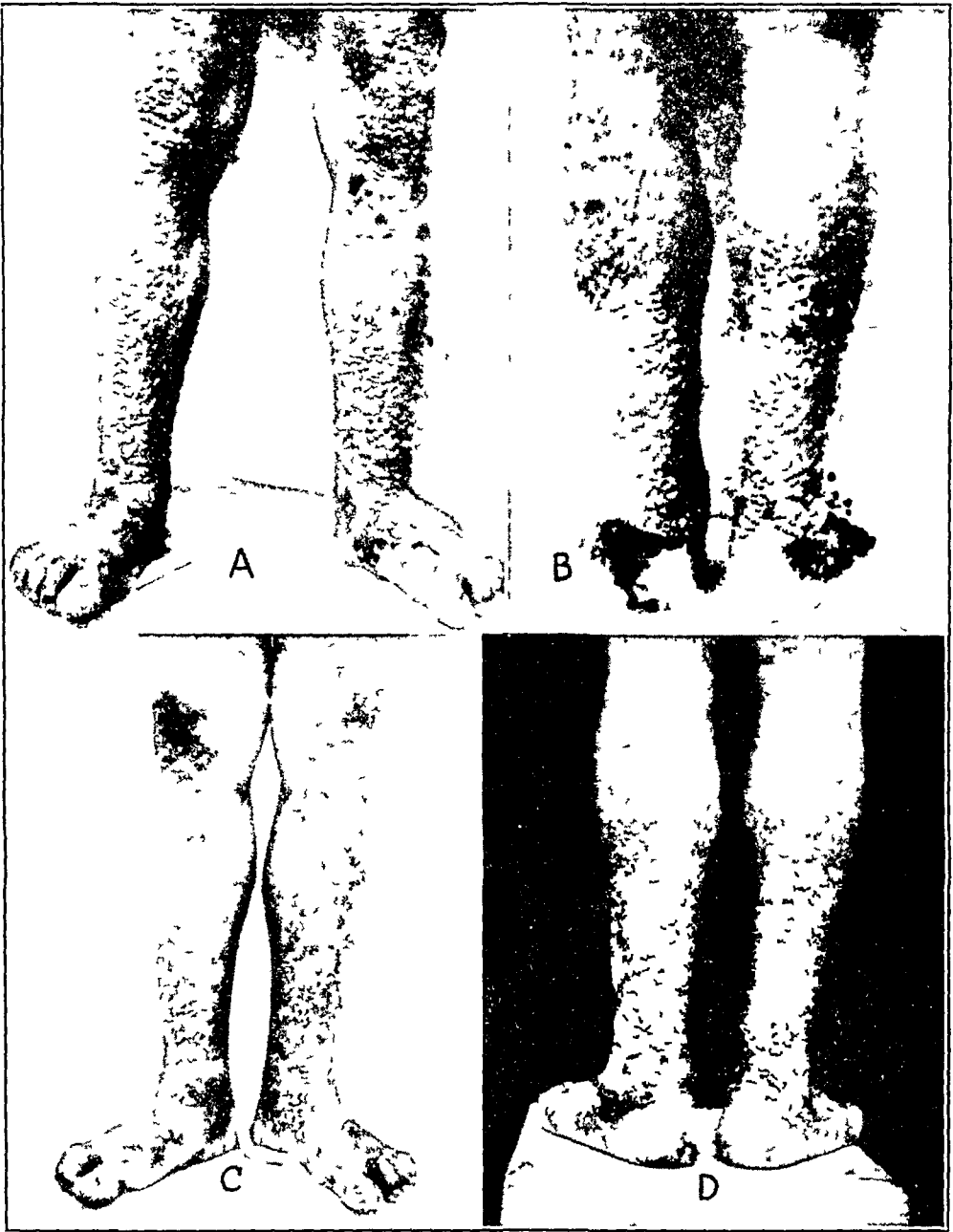


Fig 5—Unusually numerous verrugas on the skin of the legs, *A*, anterior view, *B*, posterior view *C* and *D*, regression of verrugas two months later

preted such pains as "verrucous rheumatism" due to the toxic activity of *B bacilliformis*

Paresthesias and abnormal sensations are common. Some of the patients described their sensations as "numbness," "ants walking over the skin," "burning of the skin," most often in the palms and soles,

"running electric shots" and "needles in the skin" Pruritus is often present, usually mild and transient, and often disappearing before the eruption of verrugas

The hematologic findings during this period are as follows The number of erythrocytes becomes normal in those patients who had been anemic, and no immature cells such as reticulocytes or normoblasts are observed in the peripheral blood, nor the bartonellas to be found Microcytosis was described by Hercelles¹⁷ in 1900 There is neutropenia without evidence of immature elements, the eosinophils are normal, although an eosinophilic state has been described⁵¹ The monocytes are normal in number or slightly increased and there is marked

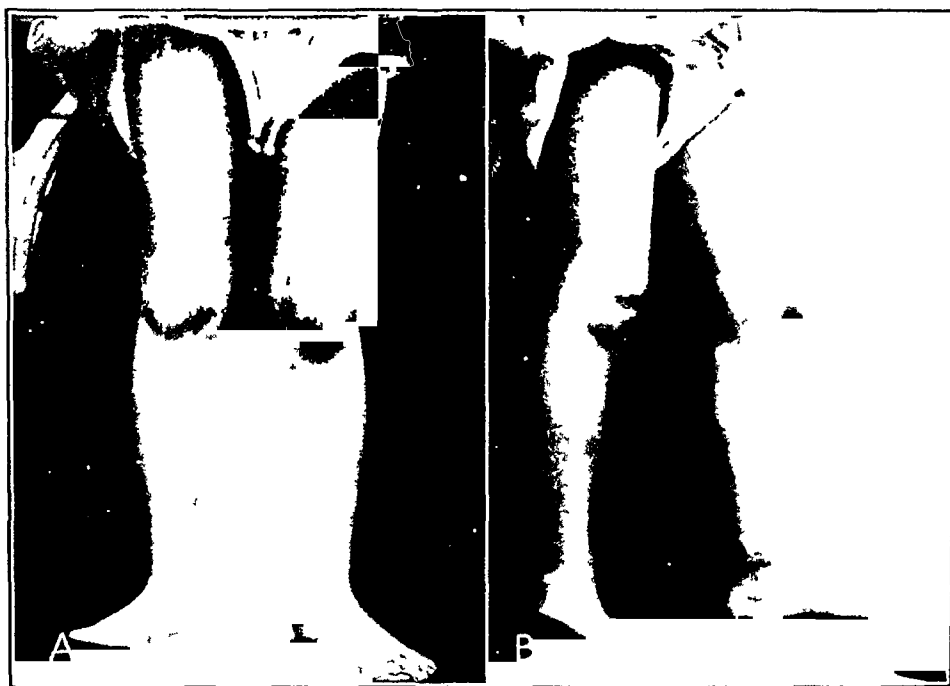


Fig 6—Protruding nodular verrugas of so-called mule type in lateral (A) and anterior (B) views

increase in lymphocytes, occasionally up to 60 and 70 per cent The number of white cells is normal, or there is a tendency toward leukopenia

The lymphadenopathy occurring during the invasive stage disappears Splenomegaly in noncomplicated cases occurs very rarely³³ but in cases with intercurrent infection is a constant finding^{37a}

4 *Eruptive Stage*—The appearance of red cutaneous nodules "the verrugas," constitutes the external pathognomonic sign of the disease They were known for many centuries, and there was a term for them in the Quechua dialect of the Peruvian Indians⁵⁷ A well developed and generalized eruption of verrugas, varying in color from red to purple,

57 Vargas-Fano⁵ Matto⁶

has distinctive characteristics unmistakable for any other disease (figs 4 to 7) Usually several months elapse from the time of the infection until the appearance of verrugas. The nodules are situated most frequently on the uncovered parts of the body and dorsal surface of the extremities but may affect the skin in other regions.



Fig 7—Enormous verruga studded with small verrugas on the elbow of an 11 year old boy. *A*, lateral view, *B*, dorsal view, *C*, dorsal aspect after resection, *D*, cut surface, demonstrating hemorrhages related to angiomatous areas.

The verrugas can be separated according to number, localization, evolution, shape, situation, size, disposition and general aspect of the eruption. They may be seen either in growth or in regression, the two stages sometimes coexisting in different verrugas in the same patient. The first clinical sign is a round, soft red papule no larger than a pin-

point that grows very rapidly in a few days or weeks. At this time it has passed from the histiocytic to the angiocytic phase. The vascularity of the nodule is easily seen upon pressure. Later they become as large as a walnut or a pear or larger. Occasionally the covering membrane is so thin that the nodule is an intense brilliant red. The florid eruption has in general been associated with a good prognosis.¹¹

The growing verrugas may in the beginning appear as very small vesicles, mimicking the aspect of a common sudamen. Later a red point appears in the center corresponding to a verruga in formation, a form carefully studied by Carrión^{10a} and later by others.⁴⁰ Mackehenie and Jimenez⁵⁸ found the specific organisms in the phlyctenular vesicles. These may become secondarily infected, resulting in a pustular form. The complete development of each nodule takes from thirty to sixty days, remaining stationary for a variable time. Salazar reported that the eruption of verrugas usually lasts from three months to one year.⁵⁹

Many studies have been made on the histopathology of the verrucous nodes.⁶⁰ Mackehenie^{60k} recognized a preeruptive histiocytic stage, an angioma-like, or angiocytic, stage and a sclerosing, or fibrocytic, stage. At the height of its development the verruga may resemble a cavernous angioma or very vascular granulation tissue. Strong¹⁷ and associates found that the typical histologic features of a verruga consist in numerous new-formed small vessels, proliferated endothelial cells and the presence of bartonellas.

The verrugas have various shapes—round, pedunculated, sessile, etc. They may be in the skin, in subcutaneous tissue or even in deeper tissue and can originate in any mesenchymal tissue. Old descriptions of the

58 Mackehenie, D, and Jimenez-Franco, J. Acerca del mosaico de poderes de la Bartonella bacilliformis, *Reforma med*, Lima **21** 677, 1935.

59 Salazar, T. Historia de las verrugas, Thesis, Lima, 1858, *Gac med de Lima* **2** 161 and 175, 1858.

60 (a) Mayer, Rocha-Lima and Werner^{16a} (b) Strong¹⁷ (c) Mackehenie²⁰ (d) Herculles⁴⁷ (e) Noguchi^{51a} (f) Mackehenie^{51e} (g) Velez, A. De las verrugas, Thesis, Lima, 1861 (h) Izquierdo, V. Spaltpilze bei der "Verruga peruana," *Arch f path Anat* **99** 411, 1885 (i) Tamayo, M. C. Histologia patológica de la verruga nodular, Thesis, Lima, 1899 (j) Escomel, E. Anatomie pathologique du verrucome de Carrión, *Ann de dermat et syph* **3** 961, 1902, *Crón méd*, Lima **20** 51, 1903 (k) Mackehenie, D. Estudio del noduloma verrucoso, *Reforma méd*, Lima **24** 50, 1938 (l) da Rocha Lima, H. Zur Histologie der Verruga peruviana, *Verhandl d deutsch path Gesellsch* **16** 409, 1913 (m) Cole, H. N. Verruga Peruviana and Its Comparative Study in Man and in the Ape, *Arch Int Med* **10** 668 (Dec) 1912, *J Cutan Dis* **31** 384, 1913 (n) Noguchi, H. Etiology of Oroya Fever. Bacterium peruvianum n sp. Secondary Invader of Lesions of Verruga Peruviana, *J Exper Med* **17** 165, 1928 (o) da Rocha, Lima, H. Verruga peruviana und teleangiectatische Granulome, *Arch f Schiffs- u Tropen-Hyg* **29** 525, 1925 (p) Letulle, M. Histologie pathologique des veruges cutanees, cited by Odriozola,¹¹ p 201.

disease⁶¹ referred to the small nodes as "miliary" verrugas, nodular or "tuberculous" verrugas, because of their resemblance to the tubercles (figs 4 and 5). The larger ones were called "mule type" (fig 6) or "tumorous type" (fig 7). In an 11 year old boy a verruga the size of a fist developed in the subcutaneous tissue of the elbow. From this tumor continuously drained serous fluid and blood until it was removed surgically. It appeared to be a very vascular angiomatous tumor, weighing 187 Gm and studded with small verrugas⁶¹.

When located in the subcutaneous tissue, the verrugas may be adherent to other tissues, such as the aponeurosis, tendons and periosteum. The subcutaneous nodules have a tendency to push out the



Fig 8—Small verruga, showing angiomatous features and perivascular infiltrates. Hematoxylin and eosin, $\times 155$.

skin, making it thin and of a purplish color. The large verrugas may have a pedicle (fig 9), partially or totally covered by the skin, and may be isolated or in conglomerates. In figure 5 there are illustrations of a patient who had a diffuse eruption of verrugas in the extremities and face. There were 1,873 verrugas on the right leg and right foot alone.

Localization of verrugas in the bones has been reported in the last century⁶² and recently⁶³. It occurred in 3 cases personally

61 Jimenez-Franco, cited by Ricketts,^{85d} p. 112.

62 Tschudi⁸ Tupper²¹.

63 Arellano, A. Primer caso clínico de localización ósea de verruga infecciosa, *Cron. med.*, Lima **12** 43, 1895.

studied³³ They have also been reported in articular and periarticular cartilages⁶⁴, in the muscles⁶¹, in the adventitia of the vessels⁶⁴, in the mucosa of the mouth,⁶⁵ respiratory tract,^{10a} esophagus and stomach⁶⁴, in the vaginal serosas⁶⁶, in the testis⁶⁶, in the capsule of the kidney, and in the epididymis⁶⁶ They have been described

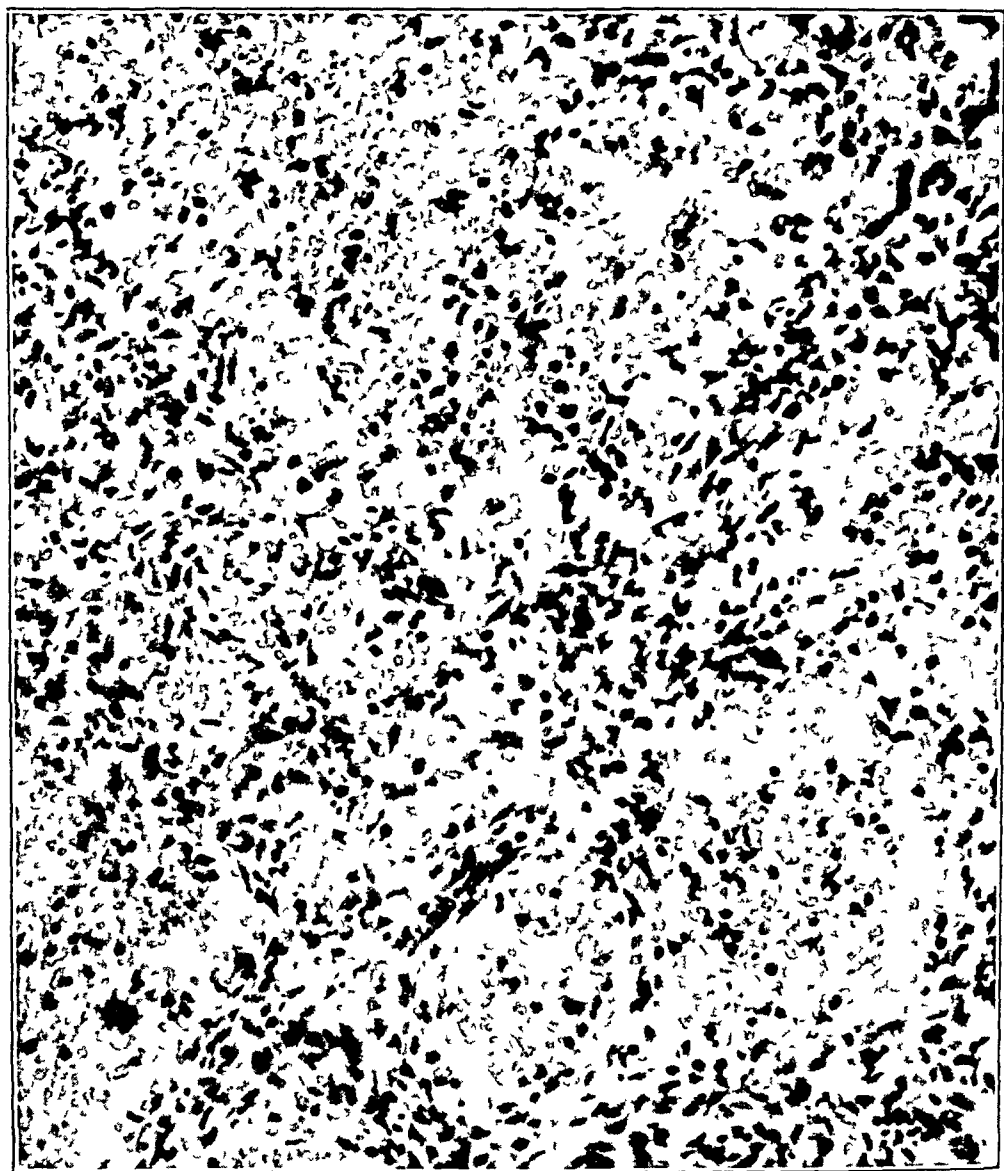


Fig 9—Section of large infected verruga, showing cavernous blood spaces Hematoxylin and eosin, $\times 300$

64 Campodonico, E Caso interesante de verruga peruana o verruga infecciosa, *Cron med*, Lima **12** 43, 1895

65 Medina^{10a} Odriozola¹¹ Campodonico⁶⁴

66 Delgado, L M El brote de verruga en la vejiga, *Rev med peruana* **7** 91-98, 1935

in the lung,⁶⁴ heart,⁶⁷ liver and spleen,⁶⁴ in several reports on glands⁶⁴ and in the brain⁶⁸ Many of the supposedly internal verrugas reported in these studies have been unaccompanied with histologic studies, a point which was emphasized by Arce²³ It is possible that many of these internal nodules described did not represent bartonella granulomas but other types of lesions

The verrugas themselves are nontender Depending on the location of verrugas, varied symptoms may occur, for instance, if the verrugas are located in either of the bronchi, hemoptysis may occur, if in the brain, epileptic seizures There is no correlation between the size of the verrugas and the local symptoms

In the regressive stage they progressively become paler because of decreased vacularization of the nodule^{60k} This represents the transition from the angioblastic to the fibroblastic stage^{60k} Occasionally they become horny, covered with a thick crust (fig 5 C and D) Tearing of the membrane of the node is followed by external hemorrhage The verrugas in the skin may leave transitorily a central hypopigmented zone, surrounded by an area of hyperpigmentation Scars are not found³³ The regression of the node is more rapid if hemorrhage, thrombosis or infection occurs within the verrugas³³ Infections of the verrucous nodes may occur focally or in systemic infections The last is hematogenous, and usually numerous nodes suppurate at the same time, *Salmonella* organisms have been isolated from these infected nodules since early in this century,⁶⁹ and Noguchi found a bacterium which he named *Bacterium peruvianum*⁷⁰

Except for pains in the joints, muscles and bones, the eruption of cutaneous verrugas is accompanied only with local symptoms Numerous general symptoms, such as fever, anemia, splenomegaly and hepatomegaly, previously pointed out as occurring in the eruptive stage, are due to secondary intercurrent infections Symptoms that are present preeruptively may change abruptly with the eruption diminishing or disappearing, and the pains in the bones, joints and muscles will fade and sometimes disappear entirely The eruption of verrugas occurs most frequently without anemia, however, in complicated cases with intercurrent infections³³ there may be anemia of varied intensity In previous studies⁴³ 3 cases were reported with a polycythemic erythrocyte count, above 6,000,000 red cells and in 1 case 7,000,000

67 Odrizola¹¹ Campodónico⁶⁴

68 González Olaechea, M Un caso de verruga infecciosa visceral, *Crón med*, Lima **7** 324, 1890

69 Biffi, U, and Carbajal, G Sobre un caso de enfermedad de Carrion con nodulomas supurados, *Crón med*, Lima **21** 285, 1904

70 Noguchi, H Etiology of Oroya Fever IX *Bacterium Peruvianum* n sp A Secondary Invader of the Lesions of Verruga Peruana, *J Exper Med* **47** 165, 1928

Lymph nodes are not enlarged except as the result of infection of the node by the organism. Under these conditions the lymph nodes may become hard, tender and tumefacient, and occasionally there is a suppurative adenitis.

"RELAPSES" OF *B. BACILLIFORMIS* ANEMIA
AND CHRONIC VERRUGAS

Patients who have had *B. bacilliformis* may later have a recurrence of symptoms with anemias one of the features. These relapses have been interpreted as relapses of the bartonella anemia, but they are, in fact, complications of several types. In these cases, *B. bacilliformis* is not found on the circulating erythrocytes. The hematologic characteristics of these secondary anemias are varied. The low erythrocyte count may be due to several factors: external hemorrhages, thrombocytopenic purpura, malaria, secondary infections and miscellaneous intercurrent infections.

Malo⁷¹ in 1852 first described the reappearance of symptoms in patients with verrugas, attributing them to the invasion of the viscera. Odriozola¹¹ made the same correlation, emphasizing the change in the appearance of the verrugas in these cases, "the eruption gets pale, atrophic and disappears rapidly." After the isolation of the causative bacteria by Barton¹³ in 1909, the recurrences associated with a high mortality were interpreted differently. It was thought that the "grave fever of Carrión" could reappear at any moment during the course of the disease,¹² an idea that has prevailed until today. The recurrence of anemia in Carrión's disease is said to be due to reinvasion of the blood by *B. bacilliformis*⁵⁴; however, no proof of such reinvasion in man has ever been offered. Experimentally, reinvasion of the red cells occurs frequently in splenectomized animals.⁷² Reinvasion of the red cells

71 Malo, N. Thesis, Santiago, 1852, *Cron. med.*, Lima **13** 201, 1895.

72 Weinman, D. Infectious Anemias Due to Bartonella and Related Red Cell Parasites, *Tr. Am. Philos. Soc.*, 1944, vol. 32, pt. 3. Levi, M., and Chiodi, V. Bartonella Anemias. Effects of Splenectomy on Structure of Erythrocytes in *Rana Esculenta*, *Sperimentale*, Arch. di biol. **88** 73, 1934. Perla, D. Compensatory Changes Following Splenectomy in Bartonella Free Rats, *Proc. Soc. Exper. Biol. & Med.* **31** 983, 1934. Domagk, G., and Kikuth, W. Development of Splenic Tissue in Liver of Splenectomized Rats and Mice as Described by M. B. Schmidt. Relation to Bartonella Infection, *Centralbl. f. allg. Path. u. path. Anat.* **59** 1, 1933. Alsted, G. Fate of Bartonella in Rats After Cessation of Anemia Following Splenectomy, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **80** 411, 1933, *Hospitaltid.* **76** 984, 1933. McCluskie, J. A. M., and Niven, J. S. F. Blood Changes in Rats and Mice After Splenectomy, *J. Path. & Bact.* **39** 185, 1934. Colichon-Arbulu, H. Infecciones espontaneas y provocadas en ratas en Lima, *Rev. méd. peruana* **6** 1611, 1934. Rhoads, C. P., and Muller, D. K. Asso-

during the eruption of verrugas would not be immunologically feasible, for bartonella anemia occurs during the invasive stage, when the immune defenses are poor, and the eruption occurs when there is a marked immunologic defense. The cases with eruption of verrugas and with a febrile anemia are probably due to intercurrent complications, such as typhoid, salmonellae infections, malaria, amebiasis, etc., as was discussed in previous papers⁷³

Carrion's disease usually confers immunity for a lifetime. Dounon⁷⁴ in 1871 asserted that the disease occurred only once. Tschudi^{8a} said that once it occurred there was a predisposition to reacquire it. Tupper,²¹ for the first time, differentiated the recurrence of the disease from the

ciation of Bartonella Bodies with Induced Anemia in Dogs, *J Exper Med* **61** 139, 1935. Knutti, R. E., and Hawkins, W. B. Bartonella Incidence in Splenectomized Bile Fistula Dogs, *ibid* **61** 115, 1935. Schwetz, J. Sur eperythrozoon coccoides. Sur des infections mixtes à Eperythrozoon coccoides et à Bartonella muris, et sur des formes bizarres et énigmatiques trouvées chez les rats et les souris sauvages de Stanleyville, *Compt rend Soc de biol* **105** 408, 1934. Bacigalupo, J. Efecto de la esplenectomia sobre las bartonellas de la sangre en rats, *Actas Cong nac med* **3** 943, 1934. Munch, O. O. Bartonella Canis Infection in Relation to Secondary Anemia and the Associated Underlying Lesions, *Am J M Sc* **191** 388, 1936. Marschall, F. Hamoglobininurie und Nierenveränderungen bei Bartonellenanämie entmilzter Ratten und bei Affenmalaria in ihrer Beziehung zum menschlichen Schwarzwasserfieber, *Arch f Schiffs- u Tropen-Hyg* **40** 151, 1936. Goyanes, J. Aspects morphologiques de Bartonella canis, *Ann de parasitol* **14** 423, 1936. Lourau, M., de Sacy, G. S., and Arthus, A. Caracteres des anemias a Bartonella muris, *Compt rend Soc de biol* **127** 1173, 1938. Lourau, M., Sacy, G. S., and Arthus, A. L'anemie a Bartonella muris caracteres et évolution. Action des facteurs hépatiques antianémiques, *Sang* **13** 749, 1939. Alsted, G. Studies on Immunity in Bartonella Anæmia, *Acta path et microbiol Scandinav*, 1938, supp 37, p 37. Lawkowicz, W. Research on Bartonella Muris. Cultivation of the Organism in Vitro, *Acta Convent tertii de trop atque malar morbis* **1** 577, 1938. Weiss, P. Contribucion al estudio comparado de las bartonellas, *Rev méd peruana* **13** 116, 1941. Lawowicz, W. Recherches experimentelles sur Bartonella muris (note preliminaire), *Bull Office internat d'hyg pub* **30** 1781, 1938. Weinman, D., and Pinkerton, H. A. Bartonella of the Guinea-Pig Bartonella Tyzzeri Sp Nov, *Ann Trop Med* **32** 215, 1938. Kessler, W. R. Studies on Experimental Bartonella Muris Anemia in the Albino Rat. II. Latent Infection and Resistance, *Jr Infect Dis* **73** 65 and 77, 1943. Carr, D. T., and Essex, H. E. Bartonellosis. Cause of Severe Anemia in Splenectomized Dogs, *Proc Soc Exper Biol & Med* **57** 44, 1944. Malo⁷¹

73 (a) Arce, J. Algunas consideraciones sobre las infecciones microbianas que complican y agravan la fiebre grave de Carrion, *Crón méd*, Lima **30** 501, 1913. (b) Tamayo, M. O. Un ensayo de clasificación de los similiticos de la verruga peruana, *ibid* **23** 295, 1906. (c) Jimenez-Franco, J. Mortalidad e interferencias en la enfermedad de Carrion, Thesis, Lima, 1938. (d) Footnotes 33, 34, 35a, 41a

74 Dounon, P. L. V. Étude sur la verruga, maladie endémique dans les Andes péruviennes, *Arch de med nav* **16** 255, 1871

frequent eruption of verrugas in nonimmunized patients Carrión^{10a} mentioned the chronic forms, and Antunez²² described such forms as are frequent in the areas where the disease is endemic I have studied cases in which a complete immunity did not occur,³³ as in 1 in which eruptions occurred three times in a ten year period Gonzalez Olachea⁷⁵ had another patient who acquired Carrión's disease and soon after remained in a place where the disease was not present Every year for twelve successive years he had an eruption of verrugas in the skin

BARTONELLA REACTIONS INDEPENDENT OF THE ERUPTION OF VERRUGAS

Inflammatory reactions localized in different tissues, such as erythemas, phlebitis, parotitis and encephalitis, are seen most frequently in the preeruptive stage of the disease³³ An erythema nodosum has been reported,⁵⁵ and Mackehenie found specific bartonella inflammations of the sebaceous follicles of the skin²⁶

Phlebitis—Phlebitis in Carrión's disease is rather uncommon It occurred in 5 out of 105 hospitalized patients, in incidence of 4.7 per cent³³ Few authors⁷⁶ have referred to the involvement of the veins in this disease Tupper²¹ in 1887 described varicose veins of the leg and considered them as sequelae of the infection Many cases have undoubtedly been misdiagnosed, as 1 labeled thrombosis of all four extremities⁵⁴ In a report of 3 cases, the distinctive characteristics of the phlebitis were analyzed⁷⁷ The general condition of the patients was found unaltered, and the conditions observed on physical examination were normal except in the areas with involved veins There was a moderate irregular temperature oscillating between 37.5 and 38.5 C (99.5 and 101.3 F), without chills and with increased pulse rate Initially, there is local perivenous inflammatory tumefaction, edema and increased temperature, but no lymphangitis or local lymphadenopathy occurred After a few days to two weeks the perivenous inflammation appeared as a hard enlarged cordlike vein There was no tendency toward invasive spreading or embolism, however, the phlebitis is frequently multiple In all 3 cases blood cultures were positive for *B. bacilliformis* when Geiman's medium was used for culture²⁸

Inflammation of the Serous Membranes—Any serous membrane, such as the pleura, pericardium and peritoneum, may exhibit nonsup-

⁷⁵ Gonzalez Olachea, M Personal communication to the author

⁷⁶ Delgado-Bedoya, G Endoplebitis verrucosa, Rev méd peruana **13** 126, 1941 Rebagliati⁴ Tupper²¹ Larrea y Quezada^{40b} Weiss⁵⁴

⁷⁷ Ricketts, W E Phlebitis in Carrión's Disease A Report of Three Cases, to be published

purative changes Pleuritis was described in the last century ¹¹ and also later ⁷⁸ González Olaechea ⁷⁹ demonstrated for the first time the presence of *B bacilliformis* in the leukocytes and macrophages of the pleural effusion The effusion is present in moderate amounts, as in 1 case in which 400 cc was removed However, clinical and pathologic evidence indicates that the effusion is due to a generalized serous inflammatory reaction and not to an internal verrugal node

Parotitis—Parotitis is quite rare, Manrique ^{41b} having described 1 case and I another, which persisted for about one month Other inflammatory reactions have also been described, such as epididymitis ⁶⁶ and iritis ⁸⁰

MENTAL AND NERVOUS SYMPTOMS

Nervous Symptomatology—Nervous and mental symptoms are not uncommon and have been attributed to neurotropic affinities of *B bacilliformis* and explained on the basis of the neurologic lesions In 1942, I attempted a classification of the nervous and mental forms of the disease ³³ This was followed by a similar study ⁸¹ Mental and nervous symptoms are usually of secondary importance and represent a minimal part of the symptomatology, however, they can constitute the dominating picture, as occurred in 11 per cent out of a series of 105 cases ³³ previously reported The central and peripheral nervous system may be involved ⁸²

Carrión suggested the possibility of localized meningeal verrugae González Olaechea ⁶⁸ described a verruga in the brain, and Campodónico ⁶⁴ reported an autopsy case with verrugas in the meninges and choroid plexus Mackehenie histopathologically proved the action of *Bartonella* on the nervous system,⁸³ and many other cases of such

78 Odrizola ¹¹ Jadassohn and Seiffert ¹⁵ Arce ³⁹

79 Gonzalez Olaechea, M Proceso pleural verrucoso en el curso de una infección verrucosa, *Rev med peruana* **5** 1331, 1933

80 Del Carpio, G Iridociclitis en la enfermedad de Carrión, Thesis, Lima, 1935

81 Lastres, J B Las neurobartonellosis 1, ensayo de interpretación etiopatogenica, *Semana méd* **2** 871, 1943

82 (a) Rossell, E Ligeros apuntes sobre la verruga peruana en el Callejon de Huailas, *Actas y trab d V Cong lat am med* **5** 198, 1914 (b) Antunez, D Distribucion geografica de la verruga peruana, *ibid* **5** 191, 1914 (c) Odrizola ¹¹ (d) Monge, C, and Mackehenie, D Formas neurologicas de la enfermedad de Carrion, *Cron med* **50** 123, 158 and 200, 1933

83 (a) Mackehenie, D, and Encinas, E Acerca de un caso de verruga benigna complicado, *Jorn neuropsiquiat Panamericana*, **2** 306, 1939 (b) Mackehenie, D, and Alzamora, V Las lesiones anatomicas del sistema nervioso en la enfermedad de Carrión, *Reforma méd*, Lima **25** 419 and 438, 1939 (c) Monge and Mackehenie ^{82d}

involvement have been reported⁸⁴ Encinas showed alterations of the nervous structures as well as the meninges in 2 cases,⁸⁵ and Quiroga-Mena⁸⁶ referred to a possible diffuse encephalopathy

Carrión was the first to describe meningeal symptoms^{10a} In several cases meningeal symptoms have developed during the invasive stage of the disease or during the critical phase of the anemia In 1 of the patients under my observation with massive parasitism of the red cells (96 per cent of the cells of the peripheral blood) and an anemia (nearly a half million red cells), the meningocephalic symptoms appeared as the last step in the progressive and fatal evolution of the bartonelosis A case of polioencephalitis was reported by me³³ in 1942, and Monge and Mackehemie^{82a} reported a choreic syndrome Paresis is not uncommon⁸⁷ In 1 case in my experience there was a transitory quadriplegia, in another a spastic paraplegia, and in a third epilepsy coinciding with the eruption of verrugas Ortiz⁸⁷ described patients with neuralgias and paresthesias who bathed in natural thermal Peruvian springs (Chancos in Carhuas and Chilcas in Mancos, Ancash, Peru) with a definite improvement I have reported a transitory paralysis of the fifth, ninth, tenth and eleventh cranial nerves before the eruption of verrugas³³ In another case polyneuritis resulted in marked muscular atrophy of the extremities Neuralgias and radicular pains are not uncommon Localized hyperhidrosis is said to be due to lesions of the vegetative nervous system,^{82a} and anatomopathologic changes in the vagus and sympathetic ganglions have also been reported^{83b}

Spinal Fluid—There are very few studies on the spinal fluid in this disease⁸⁸ In a previous analysis of 12 cases³³ with neurologic symptoms, the tensions of the spinal fluid were found normal or only slightly elevated, the fluid was transparent, alkaline in reaction without membrane formation and without coagulation The results of the chemical

84 Bello, E Verruga peruana Historia de un caso de enfermedad de Carrión, *Crón med*, Lima **10** 227, 1893 Lastres, J B Complicaciones nerviosas de la verruga peruana, *Rev méd peruana* **6** 1690, 1934, Verruga peruana y polio-mielitis anterior, *ibid* **8** 771, 1936 Méndez P, and Anglas Quintana, P Síndrome de polio-mielitis anterior aguda en el curso de la enfermedad de Carrión, *Rev neuro-psiquiat* **3** 88, 1940 Morales, A L Un caso de enfermedad de Carrión con síndrome Parkinsoniano, *Rev med peruana* **5** 646, 1933 Ricketts³³ Mackehemie and Encinas^{83a} Mackehemie and Alzamora^{83b} Monge and Mackehemie^{82a}

85 Encinas, cited by Ricketts,³³ pt 2, case reports, pp 161 and 211

86 Quiroga y Mena, R Verruga cerebral, *Crón méd*, Lima 1899

87 Ortiz, R La enfermedad de Carrión en el departamento de Ancash, *Actas y trab d V cong lat am med* **5** 648, 1914

88 Lastres, J B La cefalalgia en la verruga peruana, *Rev med san mil*, Lima **15** 11, 1942, El liquido céfalo-raquídeo en las neuro-bartonelosis, *Gac méd*, Lima **1** 104, 1945 Ricketts³³ Monge and Mackehemie^{82a}

determinations were variable. There was an increase in albumin in every patient with meningeal symptoms, in 1 the amount of albumin being 0.00230 Gm per hundred cubic centimeters. The Pandy and Nonne-Appelt reactions were sometimes strongly positive. The amount of glucose in patients with meningeal symptoms may be slightly decreased and was found to be as low as 0.22 Gm per hundred cubic centimeters in 1 case. The chlorides were not significantly lowered.

A cytologic study of the spinal fluid revealed that the cell count was normal, with the exception of cases with meningeal symptoms. In 1 case, there were 105 cells per cubic millimeter, predominantly lymphocytes, and in another, monocytes, lymphocytes, plasma cells and macrophages containing bartonellas. Guzman-Barron, cited by Monge and Mackehenie,^{76d} was the first to demonstrate the presence of *B. bacilliformis* in the spinal fluid. In a previous study³³ the colloidal gold and mastic reactions were negative in 10 cases with nervous symptoms, although in one a paralytic precipitation was complete in all the tubes. Wassermann and Kahn reactions were negative in every case.

EDEMA

Edema, which was recorded in the earliest descriptions of the disease,⁸⁹ may be generalized or local. The former may be seen over the feet or in the face, simulating kidney disease, however, the urine is normal. The blood proteins in these cases are usually low, with an inversion of the albumin-globulin ratio. In 1 such case,³⁹ the total protein was 6.97 Gm (albumin 2.36, globulin 4.61, with an albumin-globulin ratio of 0.51). Hurtado³⁰ referred the edema to the drop in the plasma albumin with resultant changes in the oncotic pressure of the blood. Merino⁹⁰ found during the acute stage of *B. bacilliformis* anemia a decrease in the amount of albumin proportional to the intensity of the anemia. He also observed that with the increase in red cells after the "critical stage" there was an increase in the amount of protein and globulin. The increase in the globulin protein fraction represents immunity against the bartonella infection.⁹⁰ After hemorrhage or protracted diarrhea, edema appears.

Localized edema in Carrión's disease without modification of the blood proteins is due to different factors, such as phlebitis, lymphatic obstruction in the vicinity of the verrugas, especially when subcutaneous nodes reach a fairly good size. Low plasma protein with an inverted albumin-globulin ratio of 0.56 in the blood coexisted in 1 case with a slight phlebitis of the saphenous vein and marked edema of the entire lower extremity.

⁸⁹ Matto.⁶ Mackehenie.²⁰

⁹⁰ Merino, C. Las seroproteínas en la enfermedad de Carrión, Thesis, Lima 1939.

PROGNOSIS

The prognosis in Carrión's disease varies considerably from patient to patient and in the different stages of the disease. The mortality occurring in *B. bacilliformis* anemia depends largely on the presence of intercurrent infections. Of 30 patients with such anemia, 9 died without demonstrable intercurrent infection. Eleven out of 15 with intercurrent infection died, an incidence of 73 per cent. One additional patient died with a coincidental rheumatic heart disease. These findings confirm previous reports⁹¹ which emphasize the importance of intercurrent infections in Carrión's disease. They occurred in 47 out of 105 cases and were responsible for death in two thirds of the fatal cases.^{35a} Jimenez-Franco, cited by me,⁷⁹ in 25 cases with autopsy found only 1 which was apparently uncomplicated. Probably the lowered resistance of the host in cases with *B. bacilliformis* anemia predisposes to fatal infections due to invasion by organisms from the gastrointestinal tract. A similar situation seems to occur in the cases complicated by amebic colitis. Parasitic infestation of the gastrointestinal tract, other than *Endameba histolytica*, does not alter the course of the disease. Malaria, the most frequent intercurrent infection, did not significantly affect the immunobiologic course of Carrión's disease. The host's defenses against intercurrent infections are not decreased during the preeruptive or eruptive stage of the disease. Of 75 patients observed during the preeruptive and eruptive stages, only 3 died, 1 with an *E. typhosa* infection and 2 with tuberculous meningitis.

TREATMENT

Until recently there has been no specific therapeutic agent for Carrión's disease, the treatment being largely symptomatic. Penicillin has recently been reported as producing good results in halting the course of the bartonella anemia.⁹² Streptomycin seems to have a similar action.⁹³ Further studies are, however, necessary to evaluate the action of these drugs in the disease.

A good deal of therapeutic effort has been directed toward stimulating the bone marrow in bartonella anemia. This is of dubious impor-

91 Ricketts³⁸ Ricketts^{37a} Alazamora-Castro^{51d} Weinman^{72a} Jimenez-Franco^{78c} Hercelles, O. Estudio de la bartonella en los organos y tejidos y deducciones que de el se sacan en el proceso anatomo-patológico de la enfermedad, Rev med peruana 7 235, 1935

92 Merino, C. Efectos de la penicilina en un caso de fiebre grave de Carrion, Gac med, Lima 1 8, 1944. Aldana, G. L., and Tisnado Munoz, S. Penicilina y enfermedad de Carrión. Estudio experimental y clínico, Rev med peruana 18 343, 1945. Merino, C. La penicilina en el tratamiento de la enfermedad de Carrión, ibid 18 329, 1945, J Lab & Clin Med 30 1021, 1945

93 Merino, C. Personal communication to the author

tance in cases without any complication, as the main problem is not to stimulate the formation of erythrocytes but to prevent the effects of their destruction. The reticulocytosis is evidence of active regeneration,⁹⁴ but it is not adequate to compensate for the extreme hemolysis. In the course of the favorable cases there is a sudden spontaneous transition with disappearance of the bartonellas from the erythrocytes. This phenomenon may give the fallacious impression that a particular drug or treatment is responsible for such change.

Blood transfusions appear to be indicated, however, up to the present they have rarely been used. This is due largely to the prevailing theory⁹⁵ that the disappearance of the bartonellas from the erythrocytes occurring during the "crisis" of the anemia is due to immunity of the red cells toward the bartonellas. Blood transfusions according to this theory will alter the immunity, since the donor cells are supposedly more susceptible and so are more apt to be parasitized. This theory is not acceptable, as the erythrocytes have never been known to have immunologic activity. The immunologic changes which occur in the host in the critical stage produce the changes both in the shape and in the clearance of the bartonellas from the erythrocytes. This is supported by the fact that the anemia does not recur in the course of the disease, even in fatal intercurrent infections occur. Small blood transfusions, 300 to 400 cc, which were available in only a few cases, proved, in my experience, to be a life-saving procedure.⁹⁶ It seems that the anemic patients with massive parasitism will greatly benefit from repeated blood transfusions as supportive therapy against the bartonella infection, the anemia and the frequent intercurrent infections. Transfusions are indicated only in this period, for when the bartonellas disappear from the erythrocytes, the destruction of red cells ceases and there is a spontaneous prompt recovery. A second therapeutic effort, such as the use of antibiotics, should be directed to prevent intercurrent infections which largely account for the high mortality in cases of B b a.

The treatment of the disease during the procrustian and eruptive stages is merely symptomatic. Patients with numerous verrugas of the extremities may have to remain in bed. For many decades local applications of various drugs to the skin⁹⁴ and administration of infusions of various plants⁹⁵ were given to produce the eruption of the verrugas, which appear to be associated with a relative immunity of the host toward the bartonella infection. These measures, however, have never

94 Escamez, E. La maladie de Carrion ou verruga du Pérou. Les dernières acquisitions, *Bull. Soc. path. exot.* 22:405, 1929. Wcinman⁷² Dounon⁷⁴

95 Maldonado, A. El escenario de la enfermedad de Carrion en el valle de Santa Eulalia y algunos datos sobre los plebotomus que la transmiten, *Crón. méd.*, Lima 50:385, 1933. Pchaghat⁴ Odriozola¹¹

been demonstrated to change the course of the infection. Large "mule" or "tumoral" verrugas may need to be removed surgically in some cases.

Immunologic therapy has not been found to be effective, nor has convalescent therapy given satisfactory results. Efforts were made however, with immune serum from rabbits, which was administered to 3 patients with bartonella anemia, in 1942.⁹⁶ In 1 of these cases, which I had the privilege of following during the succeeding year, the course of the disease was not altered. Kucziński²⁵ has properly emphasized the importance of the administration of vitamins B₁ and C in this disease.

SUMMARY

Carrión's disease and verruga peruviana are synonymous. The eponym honors Daniel Carrión, who, by self inoculation, established experimentally in 1885 the relationship between *Bartonella bacilliformis* anemia and the eruptive phase of this disease. Carrión's disease is caused by *B. bacilliformis*, a polymorphous organism classified as a bacterium, and is limited to certain zones of the Andes in Peru, Colombia and Ecuador. Clinically, it may be divided into several stages: incubative, invasive, preeruptive and eruptive with focal lesions called verrugas.

The length of the incubation period seems to vary from three to fourteen weeks, and the invasive stage varies with respect to symptoms, duration and prognosis. The onset may be insidious, with vague non-characteristic symptoms, or it may be sudden, with chills, high fever, sweating, headache and occasional delirium. Sometimes symptoms are absent altogether.

Bartonella bacilliformis anemia (Oroya fever) is a febrile hemolytic anemia with distinguishing clinical and hematologic characteristics, occurring only rarely in the invasive stage. The anemia is macrocytic and frequently hypochromic, with signs of intense blood formation. The pathognomonic sign of the disease is the presence of *B. bacilliformis* on the erythrocytes. The anemia is normoblastic, there is no spherocytosis and the saline fragility of the erythrocytes is normal. Histologically there is evidence of phagocytosis of erythrocyte in the cells of the reticuloendothelial system (the Kupffer cells and the cells lining the sinuses of the spleen and lymph nodes). There is a shift of the polymorphonuclear series to the left, characterized by the presence of myeloblasts, myelocytes and metamyelocytes. The bartonellas disappear from the erythrocytes in a very few days, and this is called the "critical stage" of the anemia. The hematologic changes of this transition are as follows: a change in the

⁹⁶ Howe, C. Studies on the Immunology of Carrion's Disease, *Arch Int Med* **72** 147 (Aug) 1943, Immune Serum Therapy in Oroya Fever, *ibid* **72** 429 (Oct) 1943.

shape of the bartonellas from the "bacilliform" to the "coccoid" form before complete clearance will take place, an increase in the erythrocyte count, reduction in the indirect hyperbilirubinemia to normal, increase in the number of monocytes and eosinophils and a "shift to the right" of the polymorphonuclear series. With the disappearance of the bartonellas from the erythrocytes, the symptoms due to the anemia vanish.

In the preeruptive stage, the symptoms are pains in the joints, muscles and bones, cramps, and paresthesias. Inflammatory reactions in various organs, such as erythemas, parotitis, phlebitis and encephalitis, occur most often in this stage. The bartonella infection may also involve the central or peripheral nervous system and the meninges.

The appearance of red cutaneous nodules, or verrugas, constitutes the pathognomonic objective clinical signs of the disease. These verrugas are usually located in the skin but may be situated in any mesenchymatous tissue. They are specific granulomas of various sizes, histologically typified by multiple newly formed small-calibered blood vessels, proliferating endothelial cells and bartonellas. Only rarely do these nodules produce local symptoms.

Carrión's disease usually confers immunity for a lifetime, although sometimes the immunity is only transitory.

The severity of the disease depends directly on the severity of the bartonella anemia, the poor prognosis being largely due to intercurrent infections of enteric origin. Until recently the treatment of this anemia has been entirely symptomatic. Preliminary studies appear to indicate that penicillin and streptomycin may halt the progress of the anemia. It is suggested that the prognosis may be improved by the use of adequate blood transfusions and the use of antibiotics.

HEPATITIS AND ITS SEQUELAE, INCLUDING THE DEVELOPMENT OF PORTAL CIRRHOSIS

Observations on One Hundred Cases

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M C F LINDERT, M D

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THE PROBLEM of hepatitis has become a very real one since the onset of World War II. Just as in and after World War I, the incidence of hepatitis and perhaps the virulence of the icterogenic substance, which has definitely been shown to be a virus, have become greater.

Our observations are presented to bring out the following points:

- 1 That the virulence of the organism during the two years previous to this report has been great, especially when it has been transmitted by the infusion of plasma or blood.

- 2 That there is a correlation between the results of liver function tests and the clinical course of the disease.

- 3 That the physician should be alert concerning the possibility of homologous serum jaundice and of syringe-transmitted hepatitis.

- 4 That chronic hepatitis and portal cirrhosis do exist as sequelae of acute hepatitis.

From July 1946 through December 1948, 100 patients with hepatitis were observed. Data on the series presented were obtained largely from the Veterans Administration Hospital, Wood, Wis., but include reports on the cases of patients seen in a large general hospital (Milwaukee County Hospital) and privately.

From the Veterans Hospital, Wood, Wis., and the Marquette University School of Medicine.

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Incidence—Of the 14,121 patients regularly admitted to the Veterans Administration Hospital during the period of this survey, 80 had hepatitis. This number represents an incidence of 0.56 per cent, which is comparable to that reported in other countries¹

Race and Sex Distribution—Of the 100 patients, 98 were white and 2 were Negro, 86 were males and 14 were females. (The males predominated in the series simply because of the preponderance of males among veterans.)

Age Distribution—The average age of the patients was 33, the youngest was 12, and the oldest was 84.

Duration of Illness—The average course of acute hepatitis was two months, while that of chronic or recurrent hepatitis was six months to five years.

It is of epidemiologic importance to note that 3 of the patients studied were physicians, 4 were nurses, 3 were medical students and 2 were laboratory technicians. Seventeen patients were exposed to blood or blood products parenterally, and 7 were subjected to hypodermic injections within four months of the acute onset of illness. Five of the latter had diabetes.

Havens² stressed the virus etiology of hepatitis because of the following factors: (1) the failure of investigators to identify a causative bacteria, (2) the production of the disease in human volunteers by the ingestion of the filtrable agents, and (3) the early development of leukopenia similar to that seen in other viral infections. Two filtrable etiologic agents have been described. These icterogenic viruses differ in the length of the incubation period, in transmissibility and that they fail to demonstrate cross immunity. The high incidence of inoculation hepatitis associated with the high mortality rate in the present group of patients studied during the postwar period renders the means of transmission of considerable importance.

We have divided the forms of the disease into three main groups: (1) infectious hepatitis, including acute and chronic or recurrent forms, (2) inoculation hepatitis, due to infected homologous serum and syringe or needle transmitted, and (3) hepatitis complicating other illnesses.

1 Stowman, K. The Epidemic Outlook in Europe, J. A. M. A. **128** 185 (May 19) 1945.

2 Havens, W. P., Jr. The Etiology of Infectious Hepatitis, J. A. M. A. **134** 653 (June 21) 1947.

Hepatitis may be caused by infectious agents other than icterogenic viruses³ The hepatitis associated with infectious mononucleosis and brucellosis was included in the study Seventy-one per cent of the patients were in group 1, 24 per cent were in group 2, and the remaining 5 per cent were in group 3 (table 1)

The diagnosis of hepatitis is not difficult In the ordinary acute attack, jaundice is the most arresting feature, this was true in 72 of our cases A careful determination of a history of past episodes of icterus is important, particularly in cases of chronic or recurrent hepatic disease Frequently a history of contact can be elicited Questions directed to obtain a history of blood transfusions, plasma infusions, venipunctures, immunizations, blood counts and hypodermic medications often provide a lead to the diagnosis of inoculation hepatitis The parenterally transmitted form of hepatitis has an average incubation

TABLE 1—*Analysis of One Hundred Cases of Hepatitis*

Type of Hepatitis	Number of Cases	Number of Deaths	Mortality Rate, Percentage
Infectious hepatitis			
Acute	45	2	4.4
Chronic or recurrent	26	0	0
Inoculation hepatitis			
Due to infected homologous serum	17	7	41.2
Due to infected syringe or needle	7	1	14.3
Hepatitis associated with infectious mononucleosis	4	0	0
Hepatitis associated with brucellosis	1	0	0

period of sixty to one hundred and twenty days, whereas it is rare for the period in the spontaneously occurring type to exceed an interval of forty-five days following contact⁴

A high percentage of the patients complained of digestive disturbances, such as anorexia, nausea, vomiting, postprandial distress and pain or distress in the right upper quadrant of the abdomen General symptoms of malaise and easy fatigability were outstanding complaints

3 (a) Capps, R. B., Sborov, V., and Barker, M. H. The Diagnosis of Infectious Hepatitis, *J. A. M. A.* **134** 595 (June 14) 1947 (b) DeMarsh, Q. B., and Alt, H. L. Hepatitis Without Jaundice in Infectious Mononucleosis, *Arch. Int. Med.* **80** 257 (Aug.) 1947 (c) Gall, E. A. Serum Phosphatase and Other Tests of Liver Function in Infectious Mononucleosis, *Am. J. Clin. Path.* **17** 529, 1947 (d) Abrams, H. L. Infectious Mononucleosis with Intense Jaundice of Long Duration, *New England J. Med.* **238** 295, 1948 (e) Cohn, C., and Lidman, B. I. Hepatitis Without Jaundice in Infectious Mononucleosis, *J. Clin. Investigation* **25** 145, 1946 (f) Morris, M. H., Robbins, A., and Richter, E. Acute Infectious Mononucleosis with Hepatitis. Presentation of Two Cases, *New York State J. Med.* **44** 1579, 1944

4 Neefe, J. R. Recent Advances in the Knowledge of "Virus Hepatitis," *M. Clin. North America* **30** 1407, 1946

The incidence of physical findings related to the hepatic disease was as follows jaundice, 72 per cent, hepatomegaly, 57 per cent, and splenomegaly in 12 per cent of the cases Hepatic tenderness or pain in the lower right portion of the thorax on percussion was frequently encountered

ACUTE INFECTIOUS HEPATITIS

The following case report illustrates acute infectious hepatitis with complete recovery

CASE 1—J W T, a white veteran and physician anesthetist of 29, entered the hospital on April 2, 1948 with complaints of nausea, vomiting, anorexia, epigastric distress, malaise, dark urine and jaundice of three days' duration On physical examination, he did not appear acutely ill but was mildly icteric The liver was palpably enlarged The responses to laboratory tests ranged as follows serum bilirubin, 0.4 to 9.4 mg per hundred cubic centimeters, icterus index, 9 to 89, thymol turbidity, 3.6 to 8.3 units, prothrombin time, 60 to 100 per cent of normal, cephalin-cholesterol flocculation, 0 to 3 plus, cholesterol-cholesterol ester ratio, 144/60, intravenous hippuric acid, 0.6 to 1.1 Gm, and two hour urinary urobilinogen, 0.3 to 3.7 Ehrlich units, and alkaline phosphatase, 7.3 to 13.6 Bodansky units per hundred cubic centimeters The blood count, urinalysis, sedimentation rate and results of serodiagnosis were not remarkable At the time of discharge, May 7, 1948, the patient's liver was no longer palpable, the jaundice had subsided, responses to all liver function tests had returned to normal and the patient was asymptomatic After a few days of graduated activity, a follow-up profile of hepatic function remained within normal limits

SYRINGE-TRANSMITTED OR NEEDLE-TRANSMITTED HEPATITIS

This form of hepatitis is no different from that classified as homologous serum hepatitis It carries this designation because it has been proved that an inadequately sterilized syringe with multiple sterilized needles may transmit the icterogenic substance

In our study of 100 patients there were 7 such instances, with a mortality rate of 14.3 per cent This disease entity was first brought to public attention in 1943, when English physicians observed considerable increase in the number of cases of hepatitis among patients being treated for syphilis in venereal disease clinics⁵ When records were carefully checked, it was noted that the incidence had increased from about 1 per cent in 1933 to as high as 50 per cent in 1945 It had

5 (a) Role of Syringes in the Transmission of Jaundice, Special Articles, *Lancet* 2 116, 1945 (b) Salaman, M H, Williams, D I, King, A J, and Nicol, C S Prevention of Jaundice Resulting from Antisyphilitic Treatment, *ibid* 2 7, 1944 (c) Darmady, E M, and Hardwick, C Syringe-Transmitted Hepatitis, *ibid* 2 106, 1945 (d) Bigger, J W Jaundice in Syphilitic Under Treatment, *ibid* 1 457, 1943

been felt that the jaundice produced in these cases was due to the reaction to the arsenic given, but it is now obvious that in many cases it was most likely due to a transmitted virus of hepatocellular disease⁶

Similar experiences have been encountered in arthritis and diabetes clinics and reported in the literature⁷ A recent report by Capps, Sborov and Scheifley⁸ described the marked increase of hepatitis in a group of persons receiving tetanus toxoid intramuscularly In our series, 5 patients who fell into this classification had diabetes and were attending the same diabetes clinic

The reports to date indicate that adequate sterilization reduces the incidence of needle transmission It has been shown that the icterogenic substance has an extreme resistance to the ordinary methods of sterilization^{6a} It has also been demonstrated that the virus is definitely inactivated or killed by sterilization with dry heat and that thirty to sixty minutes' boiling is probably effective Individual needles and syringes should be utilized in the drawing of blood and in the parenteral administration of drugs When all these measures were instituted in the diabetes clinic at the Veterans Administration Hospital, the occurrence of syringe-transmitted hepatitis was entirely eliminated

The following case report illustrates a form of inoculation hepatitis, apparently caused by an icterogenic agent transmitted by a syringe or needle and resulting in death

CASE 2—C C M, a white veteran of 52, was admitted to the hospital Jan 26, 1948 because of jaundice He gave a history of having had diabetes, which was well controlled by diet and the administration of insulin, since 1936 He was a resident of an institution where he daily attended the diabetes clinic An examination revealed generalized icterus and tenderness in the right upper quadrant of the abdomen, but the liver was not palpable The range of laboratory values was as follows serum bilirubin, 17.4 to 25 mg per hundred cubic centimeters, icterus index, 57, immediate van den Bergh reaction, positive, two hour urinary urobilinogen, 10 Ehrlich unit per cubic centimeter, thymol turbidity, 16.7 to 19.6 units, cephalin-cholesterol flocculation, 2 to 4 plus, intravenous hippuric acid, 0.15 Gm, prothrombin time was 35 to 48 per cent of normal, and cholesterol-cholesterol ester ratio, 164/28 Other values were serum albumin, 2 Gm, serum globulin, 4.3 Gm, and alkaline phosphatase, 12.5 Bodansky units per hundred cubic centimeters The urinalysis, blood count, serodiagnosis and determinations of red cell fragility, nonprotein nitrogen, blood sugar and carbon dioxide-combining power were all unremarkable The jaundice increased progressively The patient began to show sensitivity to insulin Increased breath sounds and

6 Laird, S M Syringe-Transmitted Hepatitis, *Glasgow M J* **28** 199, 1947

7 Droller, H An Outbreak of Hepatitis in a Diabetic Clinic, *Brit M J* **1** 623, 1945 Hartfall, S J Jaundice in Rheumatoid Arthritis, *Lancet* **2** 358, 1944

8 Capps, R B, Sborov, V, and Scheifley, C S A Syringe-Transmitted Epidemic of Infectious Hepatitis with Observations Regarding Incidence and Nature of Infectious Donors, *J A M A* **136** 819 (March 20) 1948

rhonchi in the left side of the chest developed, and shortly thereafter the patient went from a lethargic state into coma and died February 17. Prior to death, the size of the liver had decreased noticeably on percussion. Autopsy revealed bronchopneumonia and acute yellow atrophy of the liver secondary to hepatitis.

HOMOLOGOUS SERUM HEPATITIS

In the present series, the mortality rate in homologous serum hepatitis was notably high. Seven of 17 cases (41 per cent) terminated fatally, indicating an unusually active type of virus. Serious consideration should be given the therapeutic use of blood or blood derivatives, such as plasma, convalescent serum and biologicals to which serum has been added. Undoubtedly, blood banks try to eliminate infectious persons from their lists of donors, but the possibility of the existence of subclinical forms of hepatitis or of recent hepatitis without jaundice cannot be overlooked. It is hoped that ultraviolet irradiation of blood and blood products will, in the future, eliminate this source of infection.

The following case report illustrates a fulminating and fatal type of homologous serum hepatitis due to a virulent icterogenic virus apparently introduced in blood plasma.

CASE 3—E. D. P., a white veteran and truck driver of 21, entered the hospital Feb. 2, 1947 with a history of an infection of the upper respiratory tract followed by severe malaise, fatigue, progressive nausea and vomiting, pain in the right upper quadrant of the abdomen and dark urine of one week's duration. In December 1946 he had received 3 units of plasma during a transthoracic vagotomy for an intractable duodenal ulcer. The examination showed him to be acutely ill and icteric with tenderness in the right upper quadrant of the abdomen and a slightly enlarged liver. Laboratory values showed a range as follows: serum bilirubin, 15.7 to 19 mg per hundred cubic centimeters, cephalin-cholesterol flocculation, 4 plus, prothrombin time, 4 to 7 per cent of normal, serum albumin, 4 Gm, globulin, 2.3 Gm, alkaline phosphatase, 20.4 Bodansky units, and blood urea nitrogen, 7 mg per hundred cubic centimeters. A few tyrosine crystals were noted in a urinalysis on February 5. A complete blood count and examination of the spinal fluid were noncontributory. The sedimentation rate was normal, and blood cultures were sterile. The patient's course was rapidly downhill and was characterized by fever, lethargy, delirium, coma and death within five days after admission. An autopsy showed the cause of death to be acute yellow atrophy of the liver secondary to homologous serum hepatitis.

CHRONIC HEPATITIS

There is ample evidence provided by reliable investigators that chronic hepatitis and other sequelae may result from an acute attack of hepatitis. The incidence of chronic hepatitis is said to be low,⁹ but acute hepatitis is stated to progress to the chronic phase in from 5 to

9 (a) Lucké, B. Pathology of Fatal Epidemic Hepatitis, *Am J Pathol* 20:471, 1944, The Structure of the Liver After Recovery from Epidemic Hepatitis, *ibid* 20:595, 1944. (b) Young, L. E. Current Concepts of Jaundice with Particular Reference to Hepatitis, *New England J Med* 237:225, 1947.

50 per cent of cases¹⁰ According to Capps and his co-workers,³ a prompt reaction to the direct test for bilirubinemia almost always indicates an active phase of the chronic form of the disease, Neefe¹¹ stated that this was also the first positive sign of early acute hepatitis Although a fine distinction between chronic active and inactive hepatitis was not attempted in this series, the criteria established by Capps, his co-workers and other authors¹² were observed for the most part Twenty-six patients in our series had chronic hepatitis A history of acute hepatitis, with or without jaundice, within six months to five years of the onset of illness was obtained in each case In addition to the bilirubinemia, in most cases fairly characteristic symptoms and hepatomegaly were present and responses to one or more hepatic tests were abnormal

The following case is one of chronic and recurrent hepatitis of five years' duration, the condition showed some promise of improving

CASE 4—L J M, a white veteran and student of 27, was admitted Jan 1, 1947 with incapacitating anorexia, weakness, malaise and loss of weight He gave a past history of "catarrhal" jaundice in 1943 in New Mexico, with subsequent recurrent episodes, in Italy, in 1944 and 1945 A physical examination revealed mild, generalized icterus, a tender, firm, enlarged liver and a palpable spleen Results of the laboratory tests ranged as follows two hour urinary urobilinogen, 0 to 12 Ehrlich units, and serum bilirubin, 0.1 to 3.2 mg per hundred cubic centimeters, icterus index, 6 to 21, thymol turbidity, 4.6 to 6.4 units, cephalin-cholesterol flocculation, 0 to 1 plus, and intravenous hippuric acid, 0.3 to 1.4 Gm The sulfobromophthalein test showed 4 to 18 per cent dye retention, and the prothrombin time was 78 to 100 per cent of normal, the value for alkaline phosphatase was 4.2 to 4.5 Bodansky units per hundred cubic centimeters Repeated investigations for blood dyscrasia and for the presence of malarial and intestinal

10 (a) Capps, Sborov and Barker³ (b) Barker, M H, Capps, R B, and Allen, F W Acute Infectious Hepatitis in the Mediterranean Theatre Including Hepatitis Without Jaundice, J A M A **128**:997, 1945 (c) Volwiler, W, and Elliot, J A, Jr Late Manifestations of Epidemic Infectious Hepatitis, Gastroenterology **10** 349, 1948 (d) Klatskin, G, and Rappaport, E M Late Residuals in Presumably Cured Acute Infectious Hepatitis, Ann Int Med **26** 13, 1947 (e) Bank, J, and Cheskin, L J Hepatitis as Observed in Army General Hospital, Gastroenterology **6** 357, 1946 (f) Jersild, M Infectious Hepatitis with Subacute Atrophy of the Liver, New England J Med **237** 8, 1947

11 Neefe, J R Results of Hepatic Tests in Chronic Hepatitis Without Jaundice Correlation with Clinical Course and Liver Biopsy Findings, Gastroenterology **7** 1, 1946

12 (a) Capps, Sborov and Barker³ (b) Neefe¹¹ (c) Capps, R B The Present Status of Viral Hepatitis with Particular Reference to Chronic and Residual Forms, United States Veterans Administration Technical Bulletin 10-32, Washington, D C, Government Printing Office, May 31, 1947 (d) Atschule, M D, and Billigan, D R Chronic Latent Hepatitis Following Catarrhal Jaundice, New England J Med **231** 315, 1944 (e) Kunkel, G, Labby, D H, and Hoagland, C L Chronic Liver Disease Following Infectious Hepatitis I Abnormal Convalescence from Initial Attack, Ann Int Med **27** 202, 1947

parasites were noncontributory. Complete blood counts, and results of serologic studies and urinalyses, biopsy of a lymph node, determinations of the sedimentation rate and roentgenographic studies of the chest, gallbladder and gastrointestinal tract were normal. The patient was discharged as improved on August 9, only to present himself again in June and December of 1948 with symptoms of soreness in the right upper quadrant of the abdomen, easy fatigability, headaches and constipation. On each occasion, hyperbilirubinemia, hepatomegaly and splenomegaly were present. On the last admission, responses to all liver function tests returned to within normal limits prior to the patient's discharge from the hospital.

CHRONIC HEPATITIS

The clinical pattern of chronic hepatitis is uniformly similar to that of the acute form except for the variance in degree of the symptoms and signs, which have been well described in the literature. It may be well, however, to point out the striking symptoms and characteristic findings. Most commonly, a history of easy fatigability, mental depression and soreness, aching, fulness, heaviness or pain in the right upper quadrant of the abdomen is elicited. The last complaint is particularly noticeable after exercise or exertion. Other commoner symptoms are fat intolerance, flatulence, postprandial nausea and, occasionally, mild diarrhea. Capps^{12c} stated that the disability is often pronounced and out of proportion to the general appearance of the patients. Attempts to pursue occupations or to perform jobs that were easily accomplished before the acute episode lead to an extreme degree of fatigability. There is a tendency to relapse and remission. In a severe relapse with jaundice, the findings are usually the same as those in the acute phase. The liver is almost always palpably enlarged and tender to a variable degree. Some pain may persist in the area of the liver after a sharp blow. There may be associated splenomegaly. Laboratory tests are apt to be misleading because of the paucity of abnormal responses, but usually bilirubinemia and one or more abnormal responses to liver function tests are observed, as listed in table 2.

The symptoms may simulate a psychoneurosis¹³. Ten per cent of our patients with chronic cases were admitted to the hospital with such a diagnosis. Since the diagnosis may be extremely difficult, in many cases the disease escapes recognition, according to Barker and others^{10b}. Neefe¹¹ also found that the commonly used hepatic tests may fail to reveal hepatic disturbance in some cases in which the patients have incapacitating symptoms and for whom biopsy indicates chronic hepatitis. He stated that he considers the thymol turbidity, flocculation and colloidal gold tests the most sensitive indicators of this condition. Such was our conclusion in regard to the use of the thymol turbidity test in the present study.

13 (a) Bank and Cheskin^{10e} (b) Capps^{12c} (c) Sherlock, S, and Walshe, V. Post-Hepatitis Syndrome, *Lancet* 2 482, 1946

It is now recognized that hepatitis may persist for a long time or relapse at intervals after an initial attack¹⁴ Hepatitis that persists beyond four to six months is considered to have reached the chronic phase¹⁵ Persistent or recurrent hepatitis lasting from four months to as long as twenty-nine years after the initial onset has been described by several investigators¹⁶ In the majority of these cases, biopsies of the liver indicated hepatitis, and the patients demonstrated the characteristic symptoms (hepatomegaly and impaired responses to liver function tests)

The majority of patients with acute infectious hepatitis for whom the disease is diagnosed early and properly managed to make a complete recovery A small number die as a result of acute hepatic necrosis

14 (a) Capps, Sborov and Barker^{3a} (b) Lucké^{9a} (c) Barker, Capps and Allen^{10b} (d) Volwiler and Elliot^{10c} (e) Klatskin and Rappaport^{10d} (f) Bank and Cheskin^{10e} Jersild^{10f} (g) Neefe¹¹ (h) Capps^{12c} (i) Altschule and Billigan^{12d} (j) Kunkel, Labby and Hoagland^{12e} (k) Sherlock and Walshe^{13c} (l) Bloomfield, A. L. The Natural History of Chronic Hepatitis (Cirrhosis of Liver), *Am J M Sc* **195** 429, 1938 (m) Krarup, N B, and Roholm, K. The Development of Cirrhosis After Acute Hepatitis Elucidated by Aspiration Biopsy, *Acta med Scandinav* **108** 306, 1941 (n) Turner, R. H., Snively, J. R., Grossman, E. B., Buchanan, R. N., and Foster, S. C. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, with Special Consideration of Severe Attacks, *Ann Int Med* **20** 193, 1944 (o) Soffer, L. J., and Paulson, M. Residual Hepatic Damage in Catarrhal Jaundice as Determined by Bilirubin Excretion Test, *Arch Int Med* **53** 809, 1934 (p) Benjamin, J. E., and Hoyt, R. C. Disability Following Postvaccinal (Yellow Fever) Hepatitis. Study of Two Hundred Patients Manifesting Delayed Convalescence, *J A M A* **128** 319 (June 2) 1945 (q) Brick, I. B. Critique on Sequelae of Viral Hepatitis, *Am J Digest Dis* **15** 364, 1948 (r) Caravati, C. M. Post-Hepatitis Syndrome, *South M J* **37** 251, 1944 (s) Howard, R., and Watson, C. J. Antecedent Jaundice in Cirrhosis of the Liver, *Arch Int Med* **80** 1 (July) 1947 (t) Spellberg, M. A. Sequelae of Acute Hepatitis, *Am Pract* **2** 311, 1948 (u) Kalk, H. Chronic Forms of Epidemic Hepatitis with Regard to Their Clinical Symptomatology, *Deutsche med Wchn-schr* **72** 471, 1947 (v) Marion, D. F. Delayed Convalescence Following Acute Hepatitis. Clinical and Laboratory Evaluation, *Gastroenterology* **8** 717, 1947 (w) Flood, C. A., and James, E. M. Clinical and Pathological Findings in Prolonged Hepatitis, *ibid* **8** 175, 1947 (x) Mallory, F. B. Cirrhosis of Liver Five Different Types of Lesions from Which It May Arise, *Bull Johns Hopkins Hosp* **22** 69, 1911 (y) Kornberg, A. Latent Liver Disease in Persons Recovered from Catarrhal Jaundice and in Otherwise Normal Medical Students as Revealed by the Bilirubin Excretion Test, *J Clin Investigation* **21** 299, 1944 (z) Polack, E. Chronic Hepatitis in Young Persons With or Without Intermittent Jaundice, *Acta med Scandinav* **93** 614, 1938 (a') Snell, A. M. Fundamentals in the Diagnosis of Jaundice, *J A M A* **138** 274 (Sept 25) 1948.

15 Barker, Capps and Allen^{10b} Neefe¹¹ Capps^{12c}

16 Volwiler and Elliot^{10c} Klatskin and Rappaport^{10d} Altschule and Billigan^{12d} Flood and James^{14w}

or acute yellow atrophy This pathologic change represents the extreme lesion of viral hepatitis It is characterized by severe destruction of liver cells and an inflammatory reaction There is no alteration of the framework of the liver Scarring is not present Hyperplasia of liver cells leads to the formation of new tissues producing coarsely nodular or tumor-like lesions Healing gives rise to the so-called toxic cirrhosis, postnecrotic cirrhosis or coarsely nodular cirrhosis described by various authors¹⁷ According to Patek,¹⁸ this form of cirrhosis also may eventually terminate in fatal hepatic insufficiency

✓ PORTAL CIRRHOSIS

The relation of hepatitis to cirrhosis of the liver is still a controversial subject It is the opinion of some investigators¹⁹ that hepatitis does not lead to cirrhosis of the liver On the other hand, there is ample conclusive evidence, based on serial biopsies of the liver and on clinical observations and presented by other authors,²⁰ that hepatic cirrhosis

17 Klatskin and Rappaport^{10d} Spellberg^{14t} Mallory^{14x} Bergstrand, H Ueber die akute gelbe Leberatrophie, mit besonderer Berücksichtigung ihres Auftretens in Schweden im Jahre 1927, *Acta med Scandinav*, 1930, supp 34, p 331, *Acta path et microbiol Scandinav*, 1930, supp 5, p 41

18 Patek, A J, Jr Coarsely Nodular Cirrhosis, in Cecil, R L, McDermott, W, and Wolff, H G A Textbook of Medicine, Philadelphia, W B Saunders Company, 1947, p 867

19 (a) Lucké^{9a} (b) Klatskin and Rappaport^{10d} (c) Dible, J H, McMichael, J, and Sherlock, S V P Pathology of Acute Hepatitis Aspiration Biopsy Studies of Epidemic Arsenotherapy and Serum Jaundice, *Lancet* **2** 402, 1943 (d) Roholm, K, and Iverson, P Changes in Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, *Acta path et microbiol Scandinav* **16** 427, 1939 (e) Karsner, H Morphology and Pathogenesis of Hepatic Cirrhosis, *Am J Path* **13** 569, 1943 (f) Kalk, H, and Buchner, F Biopic Picture of Epidemic Hepatitis (Laparoscopic and Microscopic Observations), *Klin Wchnschr* **24-25** 874, 1947

20 Volwiler and Elliot^{10c} Bloomfield^{14l} Krarup and Roholm^{14m} Turner and others¹⁴ⁿ Howard and Watson^{14s} Spellberg^{14t} Kalk^{14u} Marion^{14v} Polack¹⁴⁷ Snell^{14a'} Dible, McMichael and Sherlock^{19c} Roholm and Iverson^{19d} Jones, C M, and Minot, G R Infectious (Catarrhal) Jaundice An Attempt to Establish a Clinical Entity, *Boston M & S J* **189** 531, 1923 Sherlock, A Post-Hepatitis Syndrome, *Lancet* **1** 817, 1948 Wang, E Cirrhosis of Liver and Its Relation to Acute Epidemic Hepatitis, *Nord med* **32** 2634, 1946 Findlay, G M, Martin, N H, and Mitchell, J B Hepatitis After Yellow Fever Inoculation Relation to Infective Hepatitis, *Lancet* **2**:301, 1944 Rennie, B, and Pirie, T G Infective Hepatitis with Special Reference to Prognosis, *Am J M Sc* **210** 18, 1945 Axenfeld, H, and Brass, K Klinische und biopsische Untersuchungen über sogenannten Icterus catarrhalis, *Frankfurt Ztschr f Path* **57** 147, 1942 Eppinger, H Die Leberkrankheiten, Allgemeine und spezielle Pathologie und Therapie der Leber, Vienna, Julius Springer, 1937

may be a sequela of hepatitis. It is certainly reasonable to assume that acute, chronic or recurrent hepatitis will produce hepatic damage, regeneration and fibrosis compatible with portal cirrhosis. The end result has been described in diverse fashion and under many titles. Pathologically it may be difficult to distinguish the various types, yet, clinically the important pictures are common to all at some time during the course of the disease. The relationship of clinical hepatitis to cirrhosis was substantiated by biopsies of the liver or by autopsy in 3 cases.

The following report of a case illustrates a transition of acute infectious hepatitis to portal cirrhosis.)

CASE 5—L. L. T., a white veteran and farmer of 57, entered the hospital May 14, 1948 with postprandial pain in the right upper quadrant of the abdomen, nausea, vomiting, clay-colored stools, dark urine and jaundice. He also had a past history of a chronic, recurrent duodenal ulcer. Examination showed jaundice, hepatomegaly and tenderness in the right upper quadrant. The results of laboratory studies were as follows: serum bilirubin, 0.5 to 10.8 mg per hundred cubic centimeters, icterus index, 134 to 152, two hour urine urobilinogen, 0 to 59 Ehrlich units per hundred cubic centimeters, thymol turbidity, 2.3 to 18 units, cephalin-cholesterol flocculation, 2 to 4 plus, and prothrombin time, 43 to 100 per cent of normal. The sulfobromophthalein test showed 3 per cent dye retention and the intravenous hippuric acid test 0.4 to 0.6 Gm. The value for serum albumin was 2.2 Gm, for serum globulin, 2.5 Gm, for alkaline phosphatase, 112 to 26 Bodansky units per hundred cubic centimeters. A series of fluoroscopic studies of the gastrointestinal tract revealed a duodenal ulcer. Initial blood counts, urinalyses, serologic studies and an electrocardiogram were normal. Determinations of the sedimentation rate and values for nonprotein nitrogen, blood sugar and amylase were noncontributory. (A biopsy on June 8 showed pronounced disruption of the liver architecture. There were areas in which the tissue appeared necrotic, particularly in the vicinity of the portal triad. The cord cells varied considerably in size and staining property. Nuclei of many cells were enlarged and the cell cytoplasm swollen. The cells were deeply pigmented. Bile thrombi were not seen. There was some increase in connective tissue elements. Three weeks later, a second biopsy specimen revealed less polymorphonuclear cell activity, an increase of fine, fibrous tissue and infiltrations by fibroblasts within the portal areas. These findings were consistent with early cirrhosis.) At that point, the red blood cell count gradually dropped to 2,700,000 per cubic millimeter and the hemoglobin concentration to 10.5 Gm per hundred cubic centimeters. The patient gradually improved, both from the clinical standpoint and from that of laboratory tests, although hepatomegaly persisted. He was discharged on September 29. Three months later, he remained asymptomatic and no enlargement of the liver was noted. However, the response to the cephalin-cholesterol flocculation test was 2 plus, and that to the intravenous hippuric acid test, impaired.

Lichtman, S. S. Hepatic Insufficiency, *Ann Int Med* 25:456, 1946. Watson, C. J., and Hoffbauer, F. W. Problem of Prolonged Hepatitis with Particular Reference to Cholangiolitic Type and to Development of Cholangiolitic Cirrhosis of Liver, *ibid* 25:195, 1946. Snell, A. M. Some Clinical and Physiologic Problems in Cases of Portal Cirrhosis, *North Carolina M J* 8:338, 1947.

The following case illustrates the transition of chronic infectious hepatitis of four years' duration into portal cirrhosis

CASE 6—F J L, a white veteran of 31, was admitted Feb 14, 1947 On entry, he complained of weakness, nausea, vomiting, anorexia, intolerance to fats and jaundice He gave a past history of having had hepatitis with jaundice (in North Africa) in 1943, with a recurrence in 1947 Examination showed generalized icterus with an enlarged, firm, tender liver Laboratory studies demonstrated the following values serum bilirubin, 0.4 to 3.8 mg per hundred cubic centimeters, icterus index, 9 to 26, and two hour urinary urobilinogen, 0.3 to 1.74 Ehrlich units per hundred cubic centimeters The value for the thymol turbidity test was 3.9 to 19.6 units, and that for the cephalin-cholesterol flocculation test, 0 to 3 plus, the sulfobromophthalein test showed 0 to 20 per cent dye retention and the intravenous hippuric acid test 0.61 to 0.9 Gm The prothrombin time was 60 to 100 per cent of normal The serum protein values were albumin, 3.9 to 5.4 Gm, and globulin, 2.7 to 1.8 Gm per hundred cubic centimeters, the value for alkaline phosphatase was 3.7 to 12.1 Bodansky units per hundred cubic centimeters The sedimentation rate ranged from 42 to 66 mm (Westergren method) in one hour The blood counts, urinalyses and serologic tests were not remarkable (A biopsy done on February 25 showed the liver architecture to be fairly well preserved The individual cord cells were hyperplastic and showed a slight increase in vacuolization Within the portal areas, there was a slight to moderate increase of fibrous tissue accompanied with fibroblasts and slight hyperplasia of the bile ducts Scattered lymphocytes were present in the portal areas Some liver cells were stained with bile Thrombi were not particularly evident Four weeks later, another biopsy disclosed findings compatible with portal cirrhosis The patient was discharged on April 11 and was seen again in September and in February 1948, at which times his condition was consistent with that of compensated portal cirrhosis)

✓(Another 100 patients with portal cirrhosis, whose cases are not reported here, were encountered during the study Many gave a past history of jaundice Because there was no conclusive evidence obtained to show that hepatitis was the initial hepatic disorder in these cases, the patients were not included in the series)

STUDIES OF LIVER FUNCTION

The laboratory tests most used in the series are listed in table 2 Some idea of the degree of usefulness of an individual test may be obtained by noting the percentage of cases in which the procedure was confirmatory of the clinical diagnosis For example, elevation of the value for serum bilirubin was noted in 83.8 per cent of 93 cases Nine of the 15 patients that had a normal value for serum bilirubin showed an elevated icterus index at some time during the course of illness This illustrates the importance of repeating the tests In our experience, the thymol turbidity test of Maclagan was more sensitive than that for cephalin-cholesterol flocculation, the response to the former being abnormal in 90 per cent of cases as against 75 per cent for the latter This experience is not in accordance with the findings of

Mateer and his associates,²¹ who, in an evaluation of this very point, found the cephalin-cholesterol flocculation test of Hanger to be the more sensitive and the better screening test. However, critical evaluation would depend on whether one were using the tests in acute or chronic hepatitis. The response to the thymol turbidity test is said to be more frequently abnormal in acute hepatitis, while the value for cephalin flocculation is oftener positive in chronic hepatitis and cirrhosis. Our statistics show that in 31 cases of acute hepatitis in which values for cephalin-cholesterol flocculation and thymol turbidity were both

TABLE 2—*Analysis of Pertinent Physical Findings and Laboratory Tests*

	Normal Range	Number of Cases	Cases in Which Response Was Abnormal	
			Number	Percentage
Serum bilirubin, mg per 100 cc — 1 min	0.0-2			
25 min	0.2-1.0	93	78	83.8
Jaundice		100	72	72.0
Hepatomegaly		100	57	57.0
Splenomegaly		100	12	12.0
Cephalin cholesterol flocculation (48 hr.)	0-1 plus	88	66	75.0
Thymol turbidity, units (30 min.)	0-4	60	54	90.0
Urinary urobilinogen, Ehrlich units per 100 cc (2 hr.)	0-1.0	70	51	72.8
Prothrombin time, per cent of normal	70-100	74	39	52.7
Sulfobromophthalein retention, per cent (5 mg per kg body weight, 45 min.)	0-5	42	32	76.0
Hippuric acid synthesis, Gm (intravenous)	0.7-1.0	67	38	56.7
Alkaline phosphatase, Bodansky units per 100 cc	2-6	35	23	65.7
Serum protein, Gm per 100 cc				
Total	6-8.3			
Albumin	3.8-6.1			
Globulin	1.2-3.0	57	28	49.0
Serum cholesterol				
Total, mg per 100 cc	140-250			
Esters, per cent	40-60%	14	11	78.5

determined, the former was abnormal 27 times and the latter 26 times. In such tests in 21 chronic cases, the value for cephalin-cholesterol flocculation was abnormal 10 times and that for thymol turbidity 18 times. The value for thymol turbidity remained significantly abnormal longer than the responses to any of the other liver function tests used in the study.

The prothrombin time was below normal in 52.7 per cent of 74 cases. In the majority of these cases, there was no significant rise in the prothrombin time within twenty-four to forty-eight hours after the parenteral administration of vitamin K. It is of interest to note that

21 Mateer, J. G., Baltz, J. I., Comanduras, P. D., Steele, H. H., and Brower, S. W. Further Advances in Liver Function Tests, and the Value of a Therapeutic Test in Facilitating the Earlier Diagnosis and Treatment of Liver Impairment, *Gastroenterology* 8:52, 1947.

the lowest recorded prothrombin time in the 10 cases of fatal hepatitis varied from 4 to 36 per cent of normal. Of the nonfatal cases, in only 6 was the time below 43 per cent of normal and the lowest was 33 per cent of normal. The over-all average lowest prothrombin time in the nonfatal cases was 60 per cent of normal. In our experience with hepatitis, a prothrombin level below 40 per cent of normal was of serious prognostic import.

The sulfobromophthalein test demonstrated retention of the dye in 76 per cent of 42 cases. Mateer and his co-workers²¹ classed this as one of the best of the screening tests, but it is believed to be of limited value in the presence of jaundice. Elevation of the quantity of blood phosphatase occurred in 65.7 per cent of 35 cases. Only 3 patients had elevations slightly above 20 Bodansky units per hundred cubic centimeters.

We used the test for hippuric acid synthesis (intravenous technic) in 62 cases. Patients in 56.7 per cent of this group showed impairment of this function. Values for urinary urobilinogen were abnormal in 72.8 per cent of 70 cases, the accuracy comparing favorably with that of any other liver function tests. In the determination of total cholesterol and of cholesterol esters, the ester fraction was found to be below normal in 11 of 14 cases. These tests may be of considerable value in differentiating intrahepatic and extrahepatic jaundice. We believe that had serial liver function tests been performed in all cases the percentage of abnormal tests would have been considerably higher.

MORTALITY

In general, the mortality rate in infectious hepatitis is reportedly low,¹ whereas that in homologous serum hepatitis is variable. In the epidemic of 1942, the mortality rate in 51,337 cases was 0.24 per cent.²² In the epidemic of 1943 to 1945, the mortality rate in 68,000 cases was 0.3 per cent, according to Lucké and Mallory.²³ Neefe¹¹ listed the mortality rate as ranging from 0.2 to 0.5 per cent. Contrariwise, in Jersild's^{10f} series of 550 patients the condition became chronic in 154 and of these 67 per cent died of subacute yellow atrophy. The majority of those who succumbed were in the older age group. Wood and Black²⁴ also reported a high mortality rate from serum

22 Walker, D. W. Some Epidemiological Aspects of Infectious Hepatitis in the United States Army, *Am J Trop Med* **25** 75, 1945.

23 Lucké, B., and Mallory, T. The Fulminant Form of Epidemic Hepatitis, *Am J Path* **27** 867, 1946.

24 Wood, D. A., and Black, M. B. Further Notes on Pathology of Acute Epidemic Hepatitis and Homologous Serum Jaundice, *Am J Clin Path* **16** 746, 1946.

hepatitis, particularly among wounded men. In our series, as shown in table 1, 2 of 45 patients with acute infectious hepatitis succumbed, the mortality rate was 4.4 per cent. The cause of death for 1 patient, a white man of 63, was extensive hepatic necrosis, it was revealed by autopsy. The second case was that of a white girl of 13, who presented a clinical picture of severe acute infectious hepatitis five months before death. Necropsy showed subacute hepatitis, lobular hepatic regeneration and early portal cirrhosis. Eight of 24 patients with inoculation hepatitis died, the mortality rate being 33 per cent. The mortality rate for the entire series was 10 per cent. There were no fatalities among the patients with chronic hepatitis or hepatitis of infectious mononucleosis or brucellosis during the two and one-half year period of observation.

TREATMENT

In general, the treatment outlined by Capps^{12c} was followed. It consisted of adequate rest, nutritious diet and avoidance of hepatotoxic agents. Our patients were maintained on complete bed rest until the value for serum bilirubin fell to within 1.0 mg per hundred cubic centimeters or until the jaundice cleared. With the disappearance of tenderness of the liver and the return to normal of the responses to liver function tests, the patient was permitted graduated activities. If there was no return of symptoms or change in liver function, the patient was considered to have made a complete recovery. Otherwise, complete bed rest was reinstituted.

The diet consisted of 450 Gm of carbohydrate, 150 Gm of protein and 100 Gm of fat. Until the full diet was tolerated, the parenteral administration of a 10 per cent dilution of dextrose in isotonic sodium chloride solution with soluble vitamins was considered helpful.

Methionine, given in doses of 1 to 2 Gm three times daily, appeared to have some beneficial effect in chronic hepatitis. Alcoholic beverages were interdicted. Surgical procedures were not only deferred in the acute phase but considered to be contraindicated, and intercurrent or focal infections were treated cautiously.

✓✓ SUMMARY

One hundred patients with hepatitis were observed over a period of two and one-half years. The series included cases of acute infectious hepatitis, chronic or recurrent hepatitis, homologous serum hepatitis, syringe-transmitted or needle-transmitted hepatitis and hepatitis caused by other diseases. Six representative cases are described.

The virus of homologous serum hepatitis and of needle-transmitted or syringe-transmitted hepatitis may be extremely virulent. Effective measures to combat this mode of transmission are mentioned.

The apparent transition from hepatitis to portal cirrhosis was observed in 3 cases, as manifested by the clinical course of the disease, by biopsy of the liver or by necropsy. Of the 100 patients studied, 26 had chronic or recurrent forms of hepatitis.

The significance of liver function tests is discussed. In our experience, the tests for thymol turbidity, cephalin-cholesterol flocculation and cholesterol-cholesterol ester ratio were the most sensitive in acute hepatitis. A prothrombin time below 40 per cent of normal in acute hepatitis usually signified a poor prognosis. The sulfobromophthalein and thymol turbidity tests were the best indicators of chronic hepatitis.

Treatment of hepatitis is outlined. /

Dr W A D Anderson, Professor of Pathology and Bacteriology, Marquette University School of Medicine, Dr Joseph M Lubitz, Pathologist, Veterans Administration Hospital, and Dr Joseph F Kuzma, Pathologist, Milwaukee County Hospital, made the pathologic studies in this paper.

DEFECT OF THE VENTRICULAR SEPTUM

Summary of Twelve Cases and Review of the Literature

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UNCOMPLICATED defects in the interventricular septum are among the earliest of the congenital cardiac malformations to be recognized clinically. Henri Roger presented a remarkably accurate clinical description of this syndrome in 1879,¹ and the name *maladie de Roger* is frequently used in connection with defects of the ventricular septum. Roger's presentation was in the form of a clinical lecture without the benefit of illustration by an autopsy. In spite of an abundance of reports on single cases of defect of the ventricular septum, no series was collected until 1920, when Muller² reported 9 cases and gave a brief review of case reports collected from the literature, the paper was presented in a somewhat sketchy and unsystematic manner.

The basic information about the pathologic features and the clinical picture of defect of the ventricular septum was contained in Maude Abbott's monograph³ and was based on her well known analysis of 1,000 autopsies in cases of congenital heart disease. She presented the isolated defect of the ventricular septum as a communication between the subaortic region of the left ventricle and the tricuspid area or, rarely, the conus arteriosus of the right ventricle. The defect is located in the basal part of the septum just in front of the membranous portion. Rarely, according to Abbott, defects are located in the lower, muscular part of the septum. She stated that the cardiac function is seldom interfered with, that symptoms are usually absent and that there is little change in the relative size of the ventricles and none in that of the two great arterial trunks. In contrast to all these negative factors, however, extremely loud systolic murmurs are present, the intensity

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1 Roger, H. Recherches cliniques sur la communication congenitale des deux coeurs par inoclusion du septum interventriculaire, Bull Acad de med 8 1074, 1879

2 Muller, H. Zur Klinik und pathologischen Anatomie des unkomplizierten, offenen Septum ventriculorum, Deutsches Arch f klin Med 133 316, 1920

3 Abbott, M E. Congenital Heart Disease, in Nelson Loose-Leaf Medicine, New York, Thos Nelson & Sons, 1932, vol 4, pp 207-321

of which Abbott stated varies inversely with the size of the defect. This clinical and pathologic picture of defect of the ventricular septum is essentially the one presented in most textbooks of cardiology and cardiovascular roentgenology.⁴

The presentation of the subject of defect of the ventricular septum in Taussig's recent monograph⁵ differed considerably from the conventional view, just summarized. She divided defects of the ventricular septum into "simple" defect (*maladie de Roger*) representing congenital perforation of the ventricular wall and "high" defect caused by the failure of the aortic septum to meet the ventricular septum. According to Taussig's concept, blood is shunted in the first type from the left to the right ventricle, whereas in the second type blood flows through the defect almost directly to the pulmonary artery. In the latter case, large quantities of blood may be forced into the pulmonary artery, causing its enormous dilatation. This concept of "high ventricular septal defect" as distinct from the simple defect was, however, not documented with case reports or supported with references.

Recent studies on congenital heart disease by venous catheterization of the heart have shown that considerable quantities of blood can be shunted through the defect from the left to the right ventricle.⁶ In some cases in which diagnosis was made by this method, there was considerable cardiac enlargement, which speaks strongly against the innocence of the defect as it was hitherto conceived.

The purpose of this report is to reinvestigate the subject by reviewing all available reports in the literature on cases in which autopsy was performed, also additional case reports from the files of the Department of Pathology of the Stanford University School of Medicine.

4 White, P. D. *Heart Disease*, ed. 3, New York, The Macmillan Company, 1944. Levine, S. A. *Clinical Heart Disease*, ed. 3, Philadelphia, W. B. Saunders Company, 1945. Roesler, H. *Clinical Roentgenology of the Cardiovascular System*, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1943.

5 Taussig, H. B. *Congenital Malformations of the Heart*, New York, Commonwealth Fund, 1947.

6 Handelsman, J. C., Bing, R. J., Campbell, J. A., and Griswold, H. E. *Physiological Studies in Congenital Heart Disease. V. The Circulation in Patients with Isolated Septal Defects*, *Bull. Johns Hopkins Hosp.* **82**: 615, 1948. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C., and Evans, J. M. *Studies of Congenital Heart Disease. III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect and Auricular Septal Defect*, *J. Clin. Investigation* **26**: 561, 1947. Baldwin, E. D., Moore, L. V., and Noble, R. P. *The Demonstration of Ventricular Septal Defect by Means of Right Heart Catheterization*, *Am. Heart J.* **32**: 152, 1946.

MATERIAL

The autopsy material of the department of pathology represented 7,243 autopsies performed during the period from July 1, 1932 to Dec 31, 1947. Twelve cases of uncomplicated defect of the ventricular septum were noted and are briefly summarized.

In addition, 80 reports of cases of defect of the ventricular septum in which autopsy had been performed were collected from the literature. Maude Abbott (1931) included in a table data on 55 cases, of which 52 were reviewed.⁷ This material was supplemented with more recent reports and a few additional older ones.⁸

It was thought to be of value in the presentation of some clinical features to compare defect of the ventricular septum with complete absence of the ventricular septum. For that purpose, 10 cases of trilobular heart with a single ventricle in patients who survived beyond infancy are also reviewed.⁹

7 Bauer, D de F, and Astbury, E C. Congenital Cardiac Disease. Bibliography of the One Thousand Cases Analyzed in Maude Abbott's Atlas, with Index, [References 215-240, 242-249, 251-255 and 257-260], *Am Heart J* **27**:688, 1944.

8 (a) Gallavardin, L. Maladie de Roger avec cyanose par communication interventriculaire et phthisie fibreuse, *Lyon méd* **118**:1004, 1912. (b) Laubry, C, Routier, D, and Soulié, P. Les souffles de la maladie de Roger, *Rev de méd*, Paris **50** 439, 1933. (c) Audibert, V, Raybaud, A, Giraud-Costa, Audier, and Mattéi. Endocardite maligne lente d'un orifice de communication interventriculaire, *Ann d'anat path* **9** 563, 1932. (d) Pallase. Maladie de Roger suivie pendant vingt ans, *Lyon méd* **155** 38, 1935. (e) Leech, C B. Congenital Heart Disease. Clinical Analysis of Seventy-Five Cases from the Johns Hopkins Hospital, *J Pediat* **7** 802, 1935. (f) Mason, D G, and Hunter, W C. Localized Congenital Defects of the Cardiac Interventricular Septum. A Study of Three Cases, *Am J Path* **13** 835, 1937. (g) Müller, H. Ein Fall von unkompliziertem offenem Septum ventriculorum cordis (maladie de Roger) mit grosser Lücke, *Schweiz med Wchnschr* **18** 289, 1937. (h) Seiler, S. Ueber einen Fall von Vitium Cordis Congenitum (Ventrikelseptumdefekt Pulmonalinsuffizienz), *Helvet med acta* **6** 357, 1939. (i) Congenital Anomaly of Heart. Patent Interventricular Septum, Cabot Case 25321, *New England J Med* **221** 239, 1939. (j) Ash, R, Wolman, I J, and Bromer, R S. Diagnosis of Congenital Cardiac Defects in Infancy. A Study of Thirty-Two Cases with Necropsies, *Am J Dis Child* **58** 8 (July) 1939. (k) Hanna, R. Cerebral Abscess and Paradoxical Embolism Associated with Congenital Heart Disease. Report of Seven Cases, with a Review of the Literature, *ibid* **62** 555 (Sept) 1941. (l) Tucker, A W, and Kinney, T D. Interventricular Septal Defect (Roger's Disease) Occurring in a Mother and Her Six-Month Fetus, *Am Heart J* **30** 55, 1945. (m) Welsh, K J, and Kinney, T D. The Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defect on the Development of Pulmonary Vascular Lesions, *Am J Path* **24** 729, 1948.

9 (a) von Rokitansky, C. Die Defecte der Scheidewande des Herzens, Vienna, W Braumüller, 1875. (b) Mann, J D. Cor Triloculare Batriatum, *Brit M J* **1** 615, 1907. (c) Marchand, F. Eine seltene Missbildung des Herzens eines Erwachsenen (Transposition der grossen Arterien bei rudimentärem rechten

The autopsy protocols and clinical charts were carefully reviewed. The important pathologic data included the size and weight of the heart, the size, shape and position of the septal defect, the size and position of the great vessels and their branches, the thickness of the wall of the two ventricles, and the presence of associated anomalies. The clinical data included physical findings, results of roentgenologic and electrocardiographic examination, the presence or absence of cyanosis, polycythemia and clubbing, the course, complications, and the cause of death.

Data on these factors were also assembled, whenever available, from case reports collected from the literature.

In order to extract useful information from the largest possible number of cases reported in the literature, those incompletely reported were included if the reports contained adequate information about any of the three factors: (a) size and position of the defect, (b) size of the cardiac chambers and the great arterial trunks and (c) clinical data.

All cases in which there were important malformations of the heart other than the septal defect were eliminated. However, minor congenital abnormalities were present in some cases included in this series, such as deformities or an abnormal number of the valve cusps, small patency of the foramen ovale or incomplete obliteration of the ductus arteriosus (the last two in infants), if it was thought that these associated changes had not essentially altered the cardiodynamics.

In some cases of the older group, defects of the ventricular septum were associated with acquired cardiac disease (aortic valvular disease, hypertension, etc.). Such cases were included with certain limitations. Such measurements and changes as could have been altered by the presence of secondary lesions were excluded from the tabulations.

SUMMARY OF CASES

CASE 1—M. C., a 7 year old boy, was hospitalized because of septicemia following acute otitis media. A congenital anomaly of the heart had been diagnosed at the age of 4. Roentgenographic examination at the age of 6 had revealed the heart shadow to be at the upper normal limit. During the terminal illness, physical

Ventrikel), *Verhandl d deutsch path Gesellsch* **12**:174, 1908. (d) Steinwider, C. D., and McPeak, E. M. Congenital Absence of the Interventricular Septum in an Adult Laborer. Case Report, *Texas State J Med* **25**:341, 1929. (e) Favorite, G. O. Cor Biatritum Triloculare with Rudimentary Right Ventricle, Hypoplasia of Transposed Aorta and Patent Ductus Arteriosus, Terminating by Rupture of Dilated Pulmonary Artery, *Am J M Sc* **187**:663, 1934. (f) Peters, M. Cor triloculare biatriatum mit Endocarditis lenta pulmonalis, *Centralbl f allg Path u path Anat* **62**:52, 1935. (g) Trilocular Heart, Cabot Case 28532, *New England J Med* **227**:1045, 1942. (h) Glendy, M. M. Glendy, R. E., and White, P. D. Cor Biatritum Triloculare. Case Report, *Am Heart J* **28**:395, 1944. (i) Vann, H. M., and Miller, R. E. A Case of Pseudo-Monoventricular Heart Terminating in Brain Abscess, *Anat Rec* **88**:155, 1944.

examination revealed slight cardiac enlargement, a systolic thrill in the third intercostal space at the left sternal border and a harsh systolic murmur, loudest at the same area but well heard over the entire precordium. No other abnormalities of the cardiovascular system were noted. A blood culture was positive for hemolytic streptococcus. The boy had a septic type of temperature and died in coma ten days after admission.

Autopsy revealed acute otitis media, mastoiditis with thrombosis of the jugular vein and acute nephritis. The heart appeared normal, and measurements of the four orifices and of the thickness of the ventricular walls were within normal limits for the age of the child. The ventricular septum was perforated with a small tract which when dilated measured 3 mm in diameter. It was located just underneath the posterior aortic cusp and led to the region of the tricuspid valve in the right ventricle. Other findings were of little importance.

CASE 2—E O, a girl of 14, was hospitalized because of fever and weight loss of six weeks' duration. She was known to have had heart disease since the age of 3 years and at the age of 6 was kept in bed for six months because of a "leaky valve." Examination of the patient in the hospital revealed slight cardiac enlargement. There was a systolic thrill and a loud, harsh systolic murmur at the left sternal border, loudest at the fourth costal cartilage. An early diastolic blowing murmur was heard at the same area. The blood pressure was 130 systolic and 30 diastolic, and there was a collapsing quality of the pulse.

The electrocardiogram showed a normal P-R interval, with QRS complexes measuring 0.07 seconds, tall diphasic QRS complexes (R_1 , 8 millivolts, R_2 , 13 millivolts, S_1 , 8 millivolts, R_3 , 13 millivolts, and S_3 , 12 millivolts) were noted in leads II and III. Roentgen examination was reported as revealing cardiac enlargement involving all chambers, but predominantly the left ventricle. The aortic shadow was small. There was no dilatation of the shadow of the pulmonary artery, but the hilar shadows were prominent.

The patient ran a febrile course. Blood cultures were positive for *Streptococcus viridans*. She died suddenly two weeks after admission.

Essential autopsy findings were a fatal subdural hemorrhage and septicemia due to *Streptococcus viridans*. The heart was a little larger than normal, the thickness of the cardiac muscle of the two ventricles was within normal limits. The tricuspid orifice was of normal circumference, but the valve consisted of only two cusps. Underneath the medial attachment of the cusps, there was a fistula measuring 4 mm in diameter, which entered the left ventricle just underneath the right aortic cusp. Soft, friable vegetations were present around the fistula. The pulmonary, mitral and aortic orifices showed normal measurements. The pulmonary artery was normal. There was a slight deformity of the posterior aortic cusp, which was adherent to the right cusp. A large mass of vegetations was present on the right aortic cusp overlying the septal defect, and a smaller mass, at the posterior cusp. An aneurysm measuring 11 mm in diameter was found in the anterior leaflet of the mitral valve, which was about 4 mm deep and was filled with vegetations. A small triangular opening was noted at the bottom of the aneurysm, measuring 1.5 mm on each side.

CASE 3—A man of 64 was hospitalized because of dyspnea, anorexia, insomnia and weakness, which gradually developed over a period of several weeks. He had led an active life as a plumber and had spent many years in the Orient, where he had become addicted to opium. He was said to have contracted syphilis at 45, the treatment of which consisted of only a few injections.

Examination revealed an enlarged heart and a loud systolic and an early diastolic blowing murmur over the entire precordium (heard best along the left

sternal border) The blood pressure was 120 systolic and 40 diastolic The patient's course was rapidly downhill, he lapsed into coma and died three days after admission

Pertinent autopsy findings were as follows the somewhat enlarged heart, weighing 480 Gm showed dilatation and hypertrophy of both ventricles (the pulmonary, tricuspid and mitral orifices were not remarkable), the aortic valves were almost completely filled with fresh vegetations, apparently originating on the posterior aortic cusp The other cusps were normal except for small calcified nodules A defect of the ventricular septum 7 mm in diameter was found underneath the aortic valves, it led to the area of the right ventricle underneath the tricuspid valve and was completely filled with fresh vegetations The aortic ring was somewhat stiffened by a calcific process, measuring 7 cm in diameter, but the aorta beyond it was almost completely free from atheroma A microscopic section through the septal defect showed it to be undoubtedly congenital in origin

CASE 4—A woman of 66 was known to have had heart disease since the age of 7 months and had been dyspneic on exertion since the age of 12 years At 15, she had been kept in bed for several months because of a febrile illness thought to be acute rheumatic fever Afterward, she had suffered from repeated attacks of "heart trouble," necessitating occasional periods of staying in bed for a few weeks at a time At the age of 63, frank cardiac decompensation developed, which was at first controlled by medical management, but for the last one and one half years of life the patient was a complete cardiac invalid She was known to have arterial hypertension and atrial fibrillation for at least two years before death Examination during the terminal hospitalization revealed blood pressures averaging 200 systolic and 100 diastolic and the usual signs of congestive cardiac failure The heart was enlarged to the left, and there was a systolic thrill at the apex and a harsh systolic and a blowing early diastolic murmur over the entire precordium The rhythm of the cardiac beat was completely irregular There was slight clubbing of the fingers Laboratory findings were within normal limits Hemiplegia developed, and the patient died

The autopsy, limited to the heart, showed a large organ weighing 550 Gm There was hypertrophy of both ventricles, more prominently of the right one The tricuspid ring was dilated, but the size of other orifices was within normal limits Just underneath the posterior aortic cusps, there was a defect in the ventricular septum, measuring 4 mm in diameter, which opened into the right ventricle in the region of the posterior leaflet of the tricuspid valve The defect was lined with endocardium Opposite its outlet into the right ventricle, on the anterior wall of the myocardium of the right ventricle and below the pulmonary valves, there was a patch of thickening of the endocardium measuring 3.5 by 2.5 cm

CASE 5—A baby girl was born at term and was noted to have harelip Heart sounds at the age of 1 day were not remarkable At the age of 2 weeks she was noted to become cyanotic during feeding and was found to have a loud systolic murmur and thrill over the precordium, afterward, she had frequent "cyanotic spells" A roentgenogram of the chest taken at 4 weeks showed cardiac enlargement On the twenty-eighth day, the child became more cyanotic, the temperature rose to 39.6 C (103.3 F), the respiration became rapid and she died

At autopsy, the heart weighed 75 Gm (twice normal) The foramen ovale was patent and measured 0.5 cm in diameter A large defect in the ventricular septum, measuring 1 cm in diameter, connected the region of the left ventricle below the aortic valves with the tricuspid region of the right ventricle The pulmonary artery and the aorta both measured 2 cm in diameter The two ventricles were equal in thickness of the wall, measuring 4 mm There was a small ductus arteriosus measuring 2 mm in diameter

CASE 6—A male infant was born at term and was well for three days, hematuria, melena and, finally, spasticity of both legs then developed. A systolic murmur over the precordium was noted on the fourth day. The baby died at the age of 7 days with signs of widespread hemorrhage.

At autopsy, hemorrhages were found in the lungs, kidneys and intestines. The heart weighed 30 Gm. The ductus arteriosus was patent but not more than 2 mm in diameter. The foramen ovale was patent but protected by the usual valve. Measurements of the orifices were as follows: pulmonary, 2 cm, aortic, 2 cm, tricuspid, 4 cm, and mitral, 3 cm. The walls of the ventricles measured 7 mm on the left and 3 mm on the right. A defect in the ventricular septum was located in the muscular portion, connecting the apical, lower portion of the left ventricle with the region of the posterior papillary muscle in the right ventricle. It was lined with smooth epithelium and measured 4 mm in diameter.

CASE 7—A man of 53 was hospitalized repeatedly during the last three years of life because of classic signs and symptoms of cirrhosis of the liver, associated with mild diabetes. At no time were there any symptoms referable to the cardiovascular system. On examination, the heart was usually reported as normal except for an apical systolic murmur. One observer reported a harsh systolic murmur heard over the entire precordium, about a year before the patient's death. During the terminal admission, after a severe gastrointestinal hemorrhage, a physical examination of the heart was reported as noncontributory. Slight clubbing of the fingers was noted. The patient died suddenly.

Autopsy revealed Laennec's cirrhosis of the liver with multiple esophageal varices, one of which ruptured, causing a fatal hemorrhage. The heart appeared normal on inspection and weighed 360 Gm. The foramen ovale admitted a probe but was protected by the usual flap. All the orifices and valves were normal. On the ventricular septum, 1 cm underneath the posterior aortic cusp, there were two cup-shaped depressions, one of which contained a hole 3 mm in diameter leading to the right ventricle, just underneath the tricuspid valve. The great vessels were normal.

CASE 8—A premature female infant was delivered at 8 months, weighing 2 pounds 13 ounces, she died thirteen hours after birth.

Autopsy showed cerebral hemorrhage. The heart was about normal in size. The valves, orifices and myocardium appeared normal. There was a defect in the muscular part of the ventricular septum, measuring 0.5 by 1 cm. The foramen ovale was open in only a small area.

CASE 9—A female fetus, stillborn at term, was found at autopsy to have multiple congenital defects: harelip, cleft palate, bilateral clubbed feet and Meckel's diverticulum. The heart weighed 12 Gm and appeared dilated. A 1 cm defect in the membranous portion of the ventricular septum connected the region of the left ventricle just underneath the aortic ring with the outlet of the right ventricle, being almost covered with a leaflet of the tricuspid valve. The muscular wall of both ventricles measured 2 mm, the valves were normal.

CASE 10—An apparently normal female infant died three days after birth with signs suggestive of pneumonia.

Autopsy showed partial atelectasis of the lungs. The heart weighed 20 Gm. There was a defect in the membranous part of the ventricular septum, measuring 0.8 cm in diameter. The foramen ovale was patent and had the normal flap. The cardiac valves and orifices were normal. The ductus arteriosus was patent.

CASE 11—A premature (7½ months) stillborn fetus was delivered by cesarean section, weighing 1,600 Gm.

The heart weighed 9 Gm. There was a 0.5 cm triangular defect in the membranous septum. The ventricles and valves and the great vessels appeared normal. Both orifices of the coronary arteries were moved toward the commissures between the cusps rather than occupying a portion midway between the commissures.

CASE 12—A male infant, born at term, was shown to have atresia of the esophagus and a brachioesophageal fistula. He was operated on at the age of 4 days and died eight days later with signs of respiratory difficulty.

Autopsy showed massive aspiration bronchopneumonia. The heart seemed large for the infant's size. A small hole was found in the membranous portion of the ventricular septum, otherwise, the heart and the great vessels were normal.

SUMMARY OF AUTOPSY FINDINGS IN NINETY-TWO CASES OF DEFECT OF THE VENTRICULAR SEPTUM

The 80 reports of cases of defect of the ventricular septum collected from the literature and the 12 cases reported in this paper were analyzed and the important clinical and pathologic data tabulated.

Incidence—It is exceedingly difficult to determine the frequency of congenital heart disease and the relative frequency of various malformations. The rarity of the condition makes statistics based on hospital material subject to considerable error, and, in addition, such factors as the interest of the hospital staff in the subject may influence the reliability of statistics. In order to estimate roughly the incidence of uncomplicated defect of the ventricular septum, the number of cases of this malformation was compared with the incidence of two other congenital malformations, defect of the atrial septum and tetralogy of Fallot. Table 1 presents the incidence of these three syndromes in our autopsy material as compared with other, similar series.¹⁰ It may be seen that defect of the ventricular septum and defect of the atrial septum are roughly comparable in frequency and are commoner than tetralogy of Fallot. It seems that this compilation of data, in spite of some limitations, is more reliable than Abbott's analysis of 1,000 cases based entirely on case reports from the literature. In Abbott's series, cases of tetralogy of Fallot are most numerous, those of defect of the atrial septum next and those of defect of the ventricular septum rarest of the three types. This difference is best explained by the fact that rare malformations are more readily reported in the literature than the commoner ones.

10 (a) McGinn, S., and White, P. D. Progress in the Recognition of Congenital Heart Disease, *New England J. Med.* **214**:763, 1936. (b) Philpott, N. W. Relative Incidence of Congenital Cardiac Abnormalities in Montreal Hospitals, *J. Tech. Methods* **15**:96, 1937. (c) Ingham, D. W. Congenital Heart Disease Incidence at the Mayo Clinic, *ibid.* **18**:131, 1938. (d) Clawson, B. J. Types of Congenital Heart Disease in 15,597 Autopsies, *Journal-Lancet* **64**:135, 1944. (e) Gibson, S., and Clifton, W. M. Congenital Heart Disease. A Clinical and Post-mortem Study of One Hundred and Five Cases, *Am. J. Dis. Child.* **55**:761 (April) 1938.

Age and Sex—The age of patients in this series varied from that of a premature stillborn fetus to 79 years. The sex distribution was 46 males and 42 females, the sex was not mentioned in 4 cases. The ages at death were distributed as follows: less than 1 year, 26 cases, 1 to 5,

TABLE 1—*Incidence of Defect of the Ventricular Septum, Defect of the Atrial Septum and Tetralogy of Fallot*

Source	Number of Autopsies	Patients with Defect of the Ventricular Septum (Uncomplicated)	Patients with Defect of the Atrial Septum (Including Widely Open Foramen Ovale)	Patients with Tetralogy of Fallot
Present series	7,243	12	7	9
McGinn and White ^{10a}	7,500	5	9	3
Philpott ^{10b}	7,240	11	5	10
Ingham ^{10c}	8,314	3	21	1
Clawson ^{10d}	15,597	37	7	9
Gibson and Olifton ^{10e} (infants and children only)	1,950	12	23	8
Totals	47,844	80	72	40

18, 6 to 10, 8, 11 to 15, 5, 16 to 20, 11, 21 to 30, 7, 31 to 40, 9, 41 to 50, 2, 51 to 60, 1, 61 to 70, 3, and over 70, 2

Size of Defect—Table 2 presents the size of the defect in 78 cases in which measurement of the interventricular foramen was reported. In this and the following tables, the data are presented in three age groups

TABLE 2—*Size of Defect of the Ventricular Septum in 78 Patients in Various Age Groups*

Size of Septal Defect	Patients			Total
	Under 1 Year	1 to 15 Years	Over 15 Years	
Actual diameter				
Less than 5 mm	6	10	9	25
5 to 10 mm	7	17	11	35
1 to 2 cm	4	2	7	13
Over 2 cm	1	1	3	5
Size in relation to cardiac size				
Small	1	5	9	15
Medium	4	18	11	33
Large	12	5	7	24
Extremely large	1	3	3	7

patients below the age of 1 year, those from 1 to 15 and adults (in the case of infants the value of clinical information is very limited). While division into still smaller age groups would appear desirable, it is impracticable because of the small number of cases.

The second part of table 2 represents an effort to estimate the size of the ventricular foramen in relation to the size of the heart in children. The size of the foramen was compared with the width of the aorta or

with the over-all measurement of the heart so as to make it roughly comparable to the classification adopted for fully grown hearts (0 to 5 mm diameter, small defect, 6 to 10 mm, medium-sized defect, 11 to 20 mm, large defect, and over 20 mm, extremely large defect) This is an arbitrary classification suitable only for defects of the ventricular septum, as defects in the atrial septum are, on the average, considerably larger

It is shown in the table that small and medium-sized defects are commoner than large ones, especially in the older group

Location of Defect—The important information as to the location of the defect in the ventricular septum was available in 65 cases Defects were divided in three groups (table 3) those specifically

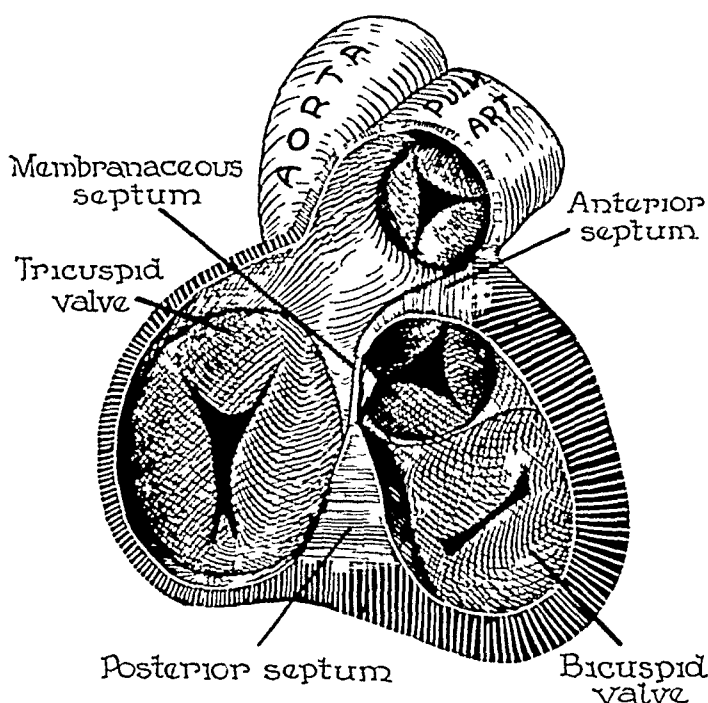
TABLE 3—*Location of Defects of the Ventricular Septum in 65 Cases in Which Autopsy Was Performed*

Location of Defect	Patients			Total
	Under 1 Year	1 to 15 Years	Over 15 Years	
1 Underneath aortic valve (in left ventricle)				
a Leading to tricuspid region of right ventricle	11	7	16	34
b Leading to conus arteriosus	0	2	2	4
c Location of opening to right ventricle unspecified	4	2	5	11
d Membranous portion of septum (multiple perforations)	0	1	1	2
2 In upper portion of septum (no more exact location reported)	3	2	3	8
Total defects in basal portion of ventricular septum	18	14	27	59
3 In lower or muscular portion of ventricular septum	3	2	1	6

described as located just beneath the aorta valve (in the left ventricle), which were instances of the typical "interventricular foramen", those described as "upper defects" without a more specific location, which are presumed to have been instances of typical interventricular foramen, and, finally, defects in the lower part of the septum, located at least 1 cm below the insertion of the aortic valve Subaortic defects were then divided into those in which the opening of the right ventricle was located close to the median leaflet of the tricuspid valve, those located more anteriorly, leading to the conus arteriosus, and those in which the location of the aperture of the right ventricle was not specified In addition, there were 2 cases in which multiple perforations of the membranous portion of the septum were reported Category 1 *a* in table 3 represents the typical interventricular foramen (Keith),¹¹ which

11 Keith, A The Hunterian Lectures on Malformations of the Heart, Lancet 2 359, 433 and 519, 1909

involves the posterior part of the anterior portion of the septum (figure) and the front part of the membranous portion of the septum. In most cases a small part of the membranous portion of the septum was still identifiable, in some it was entirely absent, and in such cases the lesion was often reported as a "defect in the undefended space." Type 1 *b* is a defect in the anterior portion of the septum, with the membranous portion of the septum intact and, usually, with muscular tissue dividing it from the defect. Both these types (1 *a* and 1 *b*) are identical with ventricular defects associated with complex malformations of the heart, notably, pulmonary stenosis and transposition of the arterial trunks.



Transverse section of the heart at the level of the membranous portion of the septum, looking up toward the great vessels (adapted from von Rokitsky^{9a})

Table 3 shows that defects in the lower septum were rare, constituting less than 10 per cent of the series.

Effect on Pulmonary Circulation—Pathologic changes usually associated with prolonged overloading of the pulmonary circulation include hypertrophy of the right ventricle, dilatation of the pulmonary artery and its branches and pulmonary arteriosclerosis. Only the first two of these three factors were considered in this series, because too few observations were made in pulmonary arteriosclerosis. The classification of hypertrophy of the right ventricle was arbitrary, in adults, the condition of the wall of the right ventricle was classified as normal if it measured less than 5 mm in thickness, if the wall measured 5 to 7 mm the condition was listed as hypertrophy and the condition of a still thicker wall was classified as severe hypertrophy. In addition,

the impression of the pathologist and—in the absence of hypertrophy of the left ventricle—the ratio of the thickness of the wall of the left ventricle to that of the wall of the right ventricle were considered in estimating the degree of hypertrophy of the right ventricle, especially in children

TABLE 4—*Relation Between Size of Defects of the Ventricular Septum and Degree of Hypertrophy of the Right Ventricle**

Size of Defect	Condition of Right Ventricle		
	Normal	Slight Hypertrophy	Severe Hypertrophy
Small	XXXX OOO	XX O	
Medium	OO	XX OOOO	X O
Large	OOO	XX OOO	XXX OOOO
Extremely large		X	XXX O

* "X" represents a patient over 15 years of age, "O," one 15 or under

Because of the physiologic preponderance of the defects of the right side of the heart and of the pulmonary circulation on that side in the fetus and in early life, the observations of the effect of defects of the ventricular septum on the pulmonary circulation were limited to patients

TABLE 5—*Relation Between Size of Defects of the Ventricular Septum and That of the Pulmonary Artery**

Size of Defect	Size of Pulmonary Artery	
	Normal	Dilated
Small	XX	XXX
Medium	OO	X OO
Large	O	XXXXXX OOOOO
Extremely large	X	X O

* "X" represents a patient over 15 years of age, "O," one 15 or under

over 1 year old Table 4 presents the relationship between the size of the defect of the ventricular septum and the degree of hypertrophy of the right ventricle in the 41 cases in which data were available on both factors It is shown that hypertrophy of the right ventricle is commonly associated with defect of the ventricular septum and that a rough relationship exists between its degree and the size of the defect

Table 5 shows a relationship between the size of the septal defect and dilatation of the pulmonary artery in 25 cases

Physical Signs—The classic sign of ventricular septal defect is the Roger murmur, a loud, long, rough systolic murmur in the third and fourth intercostal space at the left sternal border, associated with a systolic thrill in that area. In this series, reports on physical examinations were accepted in 70 cases, in the remainder they were not available or were rejected because of associated lesions. Table 6 shows the incidence and location of the murmurs in the various age groups and indicates also whether the defects were large, medium or small. The absence of any murmur was reported in 5 cases, involving 2 infants and 3 adults. In 1 case only, a diastolic murmur but no sys-

TABLE 6—*Incidence of Murmurs of Defect of the Ventricular Septum in Relation to Size of the Defect and Age of the Patient*

Murmurs	Patients											
	Under 1 Year				1 to 15 Years				Over 15 Years			
	S*	M	L	T	S	M	L	T	S	M	L	T
Systolic (at left sternal border)												
At second interspace	0	0	0	0	0	3	1	4	2	1	0	3
At third or fourth interspace	2	4	0	6	7	5	0	12	2	8	6	16
"Apical"	0	1	0	1	0	1	2	3	2	0	1	3
"Precordial"	0	4	1	5	2	2	0	4	1	6	1	8
Diastolic												
With systolic				0				2				8
Alone				0				0				1
None	0	2	0	2	0	0	0	0	0	2	1	3

* S indicates a small defect, M, a medium sized one, L, a large one, and T, the total defects in each group

tolic murmur was reported. In all other cases, systolic murmurs were noted, mostly in the classic location but occasionally higher up, in the pulmonary area, or lower, at the apex. No evidence of a change in physical signs was seen with age except in the increasing number of early diastolic blowing murmurs at the left sternal border associated with systolic murmurs. Characteristic systolic murmurs were reported as early as a few days after birth. In 4 cases the systolic murmurs were described as "soft", in most others they were loud or extremely loud. It is fully realized that data on subjective physical findings, such as cardiac auscultation, collected from many authors writing in different periods, are of limited value, nevertheless, one gathers the impression that there is no relationship between the size of the defect and the presence and intensity of the murmur, as was claimed by some, nor could the location of the murmur be definitely related to the size or anatomic position of the defect.

Cyanosis—As expected, cyanosis was absent from most cases in this series, yet, some cases reported were characterized by chronic cyanosis not associated with cardiac failure, and these deserve a careful analysis. In 2 cases¹² described as instances of uncomplicated defect of the ventricular septum, the aorta was reported as overriding the defect, and the cases were eliminated from the series as representing examples of the Eisenmenger complex. In 3 others, chronic cyanosis was reported.

Muller's case^{8g} was that of a man of 26 in whom mild to moderate cyanosis with clubbing and polycythemia had gradually developed between the ages of 20 and 23. At the age of 26 cardiac failure developed, and the patient died. He was found to have a severely hypertrophied right ventricle and a dilated pulmonary artery. A "typical" subaortic defect of the ventricular septum, measuring 1.5 cm in diameter, was found, the upper edge of which was formed by the aortic valve.

Seiler^{8h} reported the case of a woman of 22 who died of a cerebral abscess. The patient had had dyspnea and cyanosis since childhood, was somewhat underdeveloped and, at the age of 19, had been found to have the triad of moderate cyanosis, clubbing and polycythemia. In addition, there was roentgenologic and electrocardiographic evidence of severe overloading of the pulmonary circulation. The autopsy revealed prominent hypertrophy of the right side of the heart, with a dilated and sclerotic pulmonary artery and an oval defect 11 by 6 mm in the membranous septum.

Tucker and Kinney⁸ⁱ reported a case of Roger's disease in a pregnant woman of 20. She had been found to be slightly cyanotic and dyspneic at the age of 4½. She was described as showing intermittent cyanosis, particularly after exercise or exposure to cold. During pregnancy frequent attacks of extreme dyspnea and intense cyanosis developed, and the patient was found to have moderate cyanosis, clubbing and questionable polycythemia; she died in cardiac failure. Autopsy revealed marked hypertrophy of the right ventricle, but no dilatation of the pulmonary artery. A defect 2 cm in diameter was found in the typical location. A published photograph of the specimen showed the defect and the position of the aorta and suggested that the aorta may have been slightly overriding.

The summary shows that the clinical course in these 3 cases was similar to that in cases of the Eisenmenger complex. The relationship of uncomplicated defects of the ventricular septum to the Eisenmenger complex will be discussed in detail. In addition, 4 cases were reported in which there was questionable or intermittent cyanosis. There were 2 cases of children, aged 2¼ and 4½ years,¹³ with septal defects mea-

12 Lindeboom, G. A. *Morbus Caeruleus in Patient with Open Ventricular Septum*, *Nederl tijdschr v geneesk* **83** 5555, 1939. Tesseroux, H. *Zur Kenntniss der Defekte des Herzkammerscheidewand*, *Virchows Arch f path Anat* **289** 412, 1933.

13 Dupre, E. *Communication congénitale des deux cœurs, par inoclusion du septum interventriculaire avec rétrécissement de partère pulmonaire chez un jeune homme de vingt-et-un ans*, *Bull Soc anat de Paris* **66** 404, 1891. Carpenter, G. *Specimen of Congenital Morbus Cordis*, *Rep Soc Stud Dis Child* **6** 241, 1906.

suring 5 and 6 mm, respectively, the third case was that of Laubry's youth of 18,^{8b} who had a "typical" septal defect 1 cm in diameter and complicating slight aortic incompetence. He was reported to have slight cyanosis but no clubbing or polycythemia. Gallavardin^{8a} reported the case of a woman of 23 who died of pulmonary tuberculosis and who had had moderate cyanosis of unknown duration. She was found to have a large "typical" defect of the ventricular septum, a prominently dilated pulmonary artery, and severe hypertrophy of the right ventricle.

Roentgenographic and Electrocardiographic Findings—Considering the small number of case reports in which these findings were made available, only a few remarks are possible. A total of 10 reports on roentgenograms were found. In 2 of them, the heart was reported as normal. In 6 cases, cardiac enlargement was noted without a more detailed description. In 2, cardiac enlargement was associated with prominent enlargement of the pulmonary artery and its branches, presenting the configuration which is usually thought to be characteristic of defect of the atrial septum or the Eisenmenger complex, in each case, a large defect of the ventricular septum was present.

In 10 cases, reports on electrocardiographic examinations were presented. Normal curves were reported in 2 cases and right axis deviation in 3. High voltage, diphasic QRS complexes, such as were described in our case 2, were noted in 4 cases. In 1 other case, there was a typical right bundle branch block. In 4 of these 5 cases with abnormal QRS complexes, large defects were noted.

Even with this fragmentary information, it appears probable that electrocardiographic changes and roentgenographic abnormalities are likely to appear prominently in the presence of large septal defects.

Defects in the Lower Portion of the Septum—It was thought to be of importance to separate defect in the lower part of the ventricular septum, in view of Taussig's division of defect of the ventricular septum into "high" and simple types. Table 7 presents the pertinent data in the 6 cases of defects of the lower portion of the ventricular septum in this series and, in addition, in a seventh case, in which multiple perforations of the lower part of the septum were reported. The patients in 3 of these cases were newborn infants not suitable for clinical analysis. Of the remaining 4 cases, a small defect was present in 2 and a large defect in 1. In the last, hypertrophy of the right ventricle and dilatation of the pulmonary artery were reported. Murmurs were reported in 4 cases, and in 3 of them the location was given. One was reported in the typical location, 1 at the apex and 1 at the xiphoid process. It is impossible to judge from these cases whether or not an atypical location of the murmur is of diagnostic significance.

for defects in the lower portion of the septum. It appears, however, that in all other respects these cases did not present any distinctive features and that except for the location they were clinically and pathologically similar to those of other defects of the ventricular septum.

Complete Absence of the Ventricular Septum—The trilocular heart with a single ventricle is a rare malformation, an occasional survival beyond infancy has been noted. This lesion differs from simple defect of the ventricular septum only in degree and has been placed with it in a single group by one author¹⁴, yet, the complete absence of the septum and the fact that one of the great arterial trunks is usually hypoplastic alters the circulation to such a degree that only certain

TABLE 7—*Summary of Findings in Cases of Defect of the Lower Portion of the Ventricular Septum*

Source	Age and Sex of Patient	Physical Signs	Cause of Death	Size of Defect	Condition of Right Ventricle	Condition of Pulmonary Artery
Duckworth ^{13a}	Newborn M		Asphyxia	"Crow quill"		
Present series	7 days M	Systolic murmur	Hemorrhage	0.5 cm	Normal	Normal
Present series	13 hours F		Hemorrhage	0.5 by 1 cm		Normal
Muller ^{8c}	1 yr., 9 mo M	Systolic murmur at third rib, left sternal border	Broncho pneumonia	3 mm	Dilated	Enlarged
Mason and Hunter ^{8f}	12 years M		Unknown (sudden death)	1 by 0.8 cm	Hypertrophy	Dilated
Carey ^{13a}	37 years M	Systolic murmur at apex	Cirrhosis of liver	4 mm	Normal	
Weiss ^{13a}	79 years M	Systolic murmur at xiphoid process	Uremia	Small (multiple)	Normal	Normal

clinical features can be compared in these two syndromes. Those which were thought to be useful for the analysis of the clinical features of defect of the ventricular septum were as follows: (a) the presence of systolic murmurs in the trilocular heart, (b) the presence or absence of cyanosis, and (c) the incidence of conduction defects in the electrocardiogram.

The patients in the 10 cases of trilocular heart died at the ages of 8 to 36 years. For 8 of the cases, a report on physical findings was

^{13a} Cited by Bauer and Astbury.⁷

¹⁴ Schnitzler, M. A. *The Electrocardiogram in Congenital Cardiac Disease. A Study of One Hundred and Nine Cases, One Hundred and Six with Autopsy*, Cambridge, Mass., Harvard University Press, 1940.

available, and in all these, loud systolic murmurs were present. The location was reported as "precordial" in 3, "apical" in 2 and "pulmonary" in 3. In 4 cases, diastolic murmurs were also heard.

Cyanosis was present in all cases except 1, in which it was questionable. In 7 cases, cyanosis was severe and had been present since childhood. In 2 cases, it appeared late and was mild.

Electrocardiograms were described in 4 cases. In all of them, tall, wide, diphasic QRS complexes were reported.

Associated Lesions—Whereas major associated congenital malformations were eliminated by excluding cases of these disorders from the series of cases of defect of the ventricular septum, a number of defects were present which were thought to be of little importance from the standpoint of cardiodynamics. The distribution of these associated lesions was as follows: anatomic patency of the foramen ovale, 12 cases, incomplete obliteration of the ductus arteriosus (cases with widely patent ductus were eliminated), 4, bicuspid pulmonary valves, 2, bicuspid aortic valves, 3, retraction and deformity of the posterior aortic cusp, 3, deformity of the median tricuspid leaflet, 3, and right-sided aortic arch, 1.

Cases of acquired cardiac lesions included 4 of calcific aortic stenosis, the lesions in 3 of them being superimposed on bicuspid valves. In 2 cases, rheumatic endocarditis was diagnosed, involving the mitral valve in 1 and the mitral and tricuspid valves in the other. In none of these cases of acquired valvular lesions were the deformities severe. Bacterial endocarditis involved, in addition to the interventricular foramen, the pulmonary valve in 5 cases and the aortic valve in 4.

Prognosis—The prognosis in congenital cardiac malformations was expressed by Abbott in terms of the average duration of life in her series of cases collected from the literature. It gave, however, a misleading impression, since the calculation was influenced by the large number of infants. It was thought that a much fairer view of the severity of the lesion could be presented by means of an analysis of the causes of death in a series of cases, with an effort being made to separate the cases in which the causes of death were directly related to the malformation from those in which the patient died from unrelated causes. Such an analysis is presented for the series of cases of defect of the ventricular septum in table 8, in which the incidence of death from the four commonest causes in congenital heart disease is contrasted with that from coincidental and unrelated causes. Cardiac failure was responsible for a moderately small number of deaths, whereas bacterial endocarditis appeared a more important hazard. Pulmonary tuberculosis and cerebral abscess were relatively unimportant. The majority of patients died of causes unrelated to the cardiac malformation, mostly noncardiac.

It is fully realized, however, that the presence of cardiac disease in these cases may have been a contributory factor in some of these unrelated deaths, the importance of which cannot be estimated.

Pursuing this line of reasoning further, it was noted that of the 6 adults who died of cardiac failure, the oldest was 66. Two patients had complicating hypertension. The duration of cardiac insufficiency

TABLE 8—Cause of Death in 85 Cases of Defect of the Ventricular Septum in Relation to Age Groups

Cause of Death	Patients				
	Under 1 Year	1 to 15 Years	Over 15 Years	Total	
				Number	Percentage
Cardiac failure	1	6	6	13	15
Bacterial endocarditis	0	9	9	18	20
Tuberculosis of lungs	0	1	4	5	6
Cerebral abscess	0	1	2	3	4
Other causes	20	11	15	46	55

from onset to death varied from a few weeks to two years. One patient had atrial fibrillation.

COMMENT

Pathogenesis of Defect of the Ventricular Septum—Defects in the ventricular septum have attracted less attention as isolated lesions than in combination with other malformations. Von Rokitsansky^{9a} presented in his classic monograph on defects of the cardiac septums 24 reports of cases of defect of the ventricular septum, but in all of them associated malformations were present. He concluded that other defects, notably pulmonary stenosis and the overriding aorta, are the primary cause and that the defect of the ventricular septum is the result of combined malformations. This view has been accepted with modifications ever since. The most important question in connection with the series of cases analyzed in this paper is whether the pathogenesis of uncomplicated defect of the ventricular septum is basically different from that of septal defects constituting a part of the tetralogy of Fallot or similar syndromes. This question has never been answered, nor has it been studied carefully. Keith,¹¹ states that cases of uncomplicated defect of the ventricular septum deserve further study, and Spitzer,¹⁵ in his extensive monograph, made only a brief mention of simple defects.

¹⁵ Spitzer, A. Ueber den Bauplan des normalen und missbildeten Herzens. Versuch einer phylogenetischen Theorie, Virchows Arch f path Anat **243** 81, 1923.

It is shown in this report that the great majority of uncomplicated defects of the ventricular septum are located immediately underneath the aortic valve. This location of the defect is identical with those constituting a part of complex cardiac malformations.

One of the most important contributions to the study of congenital heart disease is the work of Spitzer,¹⁵ who studied the phylogenetic and ontogenetic mechanism of certain cardiac malformations and postulated a uniform mechanism of all defects associated with various types of transposition of the arterial trunks. He included in his concept of transposition the overriding of the aorta over a septal defect (Spitzer's type 1) and showed that within this type there is a considerable variation in the position of the aorta. In his series of cases of transposition, cases were included in which the aorta originated almost completely from the left ventricle (only one tenth of it was over the right ventricle). In such cases (no 1 and 2 in Spitzer's report), the defect of the ventricular septum was for practical purposes "uncomplicated," since no associated malformations were present. Spitzer noted that smaller septal defects are usually associated with a lesser degree of overriding. He provided a common explanation for all malformations associated with any form of transposition in the theory of faulty torsion (detorsion) of the primitive cardiac tube.

Spitzer's theory has been generally accepted as the foundation of the modern knowledge of cardiovascular malformation, although some details of his theory have been criticized and modified.¹⁶ It provides a basis for the unified classification of all subaortic defects of the ventricular septum regardless of associated lesions. It is possible that the process of maldevelopment (Spitzer's detorsion) causes in mildest cases small, uncomplicated defects of the ventricular septum, in more advanced cases defects combined with dextraposition of the aorta (Eisenmenger complex) with or without pulmonary stenosis (tetralogy of Fallot) and in most severe cases transposition of the arterial trunks (Spitzer's types 2, 3 and 4). This concept would place most cases of simple defect of the ventricular septum in the group of "transposition malformations," and it could perhaps be proved correct if other criteria of transposition than the position of the aorta (malposition of the coronary ostia and of the bulbar ridges) were found in some of these

16 Pernkopf, E., and Wirtinger, W. Die Transposition der Herzostien—ein Versuch der Erklärung dieser Erscheinung, *Ztschr f Anat u Entwicklungsgesch* **100** 563, 1933. Harris, J. S., and Farber, S. Transposition of the Great Cardiac Vessels, with Special Reference to the Phylogenetic Theory of Spitzer, *Arch Path* **28** 427 (Oct) 1939. Lev, M., and Saphir, O. A Theory of Transposition of the Arterial Trunks Based on the Phylogenetic and Ontogenetic Development of the Heart, *ibid* **39** 172 (March) 1945. Saphir, O., and Lev, M. The Tetralogy of Eisenmenger, *Am Heart J* **21** 31, 1941.

cases 'To date, detailed studies of cases of uncomplicated ventricular septal defect are not available. One can, however, speculate by presenting arguments favoring such a concept. (a) It has been noted that a great majority of uncomplicated defects of the ventricular septum are identical in position and shape with those associated with, and caused by, dextraposition of the aorta, it appears unlikely that two different developmental errors would cause exactly the same morphologic changes. (b) The dividing line between simple defects of the ventricular septum and those combined with dextraposition (Eisenmenger complex) is indistinct¹⁷. Many patients reported as having Eisenmenger complex showed only minimal overriding of the aorta and could have been classified by some pathologists as having simple defects of the ventricular septum. Some patients reported as having defects of the ventricular septum, on the other hand, would have been better classified as having the Eisenmenger complex. There is obviously a transitional zone in which the pathologist finds it difficult to decide whether the position of the aorta justifies a classification of "overriding". The gradual transition between a septal defect with a normal position of the aorta and one with an unquestionable dextraposition suggests a common etiologic factor. (c) Even in the tetralogy of Fallot, which is the commonest and best known type of complex cardiac malformation, there are instances in which the aorta originates almost entirely from the left ventricle, and in which the morphologic appearance of the specimen indicates pulmonary stenosis combined with a simple ventricular septal defect. This also favors a common pathogenesis of all subaortic ventricular septal defects.

In considering the relationship between the Eisenmenger complex and simple defect of the ventricular septum, one should note the normal topographic relationship of the base of the aorta to the ventricular septum, as indicated in the illustration. The posterior portion of the anterior part of the septum and the anterior portion of the membranous part of the septum are located immediately underneath the aortic orifice. If these two parts of the septum are defective, the aorta comes in close contact with the right ventricle. Dextraposition and overriding could therefore be caused not only by an embryologic rotation of the aorta to the right but, perhaps, also by acquired changes developing in extrauterine life, such as deviation of the septum to the left or slight rotation of the aortic orifice on a posteroanterior axis¹⁷.

Defects other than subaortic ones originate by a different process of maldevelopment, probably an imperfect formation of the muscular portion of the septum. These defects are rare, and clinically they do not present a distinctive syndrome.

17 Selzer, A., and Laqueur, G. The Eisenmenger Complex, to be published

Effect of Defect of the Ventricular Septum on the Circulation—Clinically, defect of the ventricular septum is usually pictured as a “functionally silent” lesion with little alteration of cardiodynamics¹⁸ This view would suggest that a fistulous connection between the two ventricles is of lesser importance than one between the atriums or between the arterial trunks, for both in defect of the atrial septum and in patent ductus arteriosus circulatory dynamics usually show considerable changes It is evident from the results of the analysis of this series that such a view is incorrect Pathologic findings in a large proportion of cases show changes indicative of considerable overloading of the pulmonary circulation It has been shown that changes such as hypertrophy of the right ventricle and dilation of the pulmonary artery are related to the size of the defect and not to the position of it, as suggested by Taussig In this connection, it is well to recall that acquired perforations of the ventricular septum, which occasionally occur in the course of acute myocardial infarction and are located in the muscular portion of the septum, are known to be associated with severe dilatation and failure of the right ventricle

Whereas a defect of the ventricular septum, if large enough, may have a striking effect on the circulation, such large defects are less common than smaller ones This preponderance of smaller defects which need not alter circulatory dynamics seems to be the reason for the older view that ventricular septal defect is an innocent cardiac malformation The frequency of smaller defects is in line with the view expressed in the preceding paragraph, that large defects are caused by severer malrotation of the cardiac tube and, therefore, are more likely to occur in complex cardiac malformation than as isolated lesions

Cyanosis—In the presence of a normal relationship of pressure between the ventricles, oxygenated blood flows back into the right ventricle through the defect and cyanosis is absent, yet, chronic cyanosis associated with polycythemia and clubbing has been reported in some cases of allegedly uncomplicated ventricular septal defect Since, at the time of writing, nobody has proved the existence of a deficiency in the oxygen exchange in the lungs in congenital cardiac malformation, it is believed that cyanosis is due to the admixture of venous blood in the arterial system The reason for the entry of venous blood into the left ventricle is not clear Whereas the pressure in the right ventricle may be considerably increased and true pulmonary hypertension may be present in patients with overloaded pulmonary circulation, it is doubtful whether pressure in the right ventricle

¹⁸ Laubry, C, and Pezzi, C *Traité des maladies congénitales du cœur*, Paris, J.-B. Ballière & fils, 1921

could permanently exceed that in the left ventricle. In addition, every evidence points to the fact that the output of the right side of the heart considerably exceeds that of the left side, indicating a large over-all left to right blood shunt. One could postulate the presence of turbulence in the defect, allowing the free mixing of blood from both ventricles, this mechanism of cyanosis is the obvious one in hearts with a single ventricle. However, the size of the typical interventricular foramen makes the free mixing of blood in the presence of a large left to right fistula somewhat unlikely, for these defects seldom exceed 2 cm in diameter and are considerably smaller than defects in the atrial septum. It should also be noted that cyanotic cases in this series were not necessarily those in which the largest defects occurred. The most likely factor facilitating the mixing of blood in the defect is the anatomic position of the aorta overriding the defect, in the presence of a large enough foramen and, perhaps, of high pressure in the right ventricle. The view has been expressed that in borderline cases overriding of the aorta could develop later in life and need not be due to congenital dextraposition. It is believed, then, that the presence or absence of cyanosis is the criterion distinguishing simple ventricular septal defect from the Eisenmenger complex, and one which may be more accurate than examination of the pathologic specimen. One can thus postulate that in cases of large ventricular septal defects located immediately underneath the aortic orifice, the presence of normal oxygen saturation of arterial blood justifies the classification of "uncomplicated ventricular septal defect" whereas the presence of arterial anoxemia calls for inclusion in the Eisenmenger group. This statement is based on the fact that morphologically there is no distinct dividing line between the two syndromes, and that the clinical, electrocardiographic and roentgenographic features of large ventricular septal defects and of the Eisenmenger complex are identical.

Little light is thrown on the question of *cyanose tardive*, or cyanosis due to the terminal reversal of the blood flow in the shunt. Such terminal cyanosis has been reported in a few cases, but it is exceedingly difficult to judge whether cyanosis appearing in the course of cardiac failure is more intense than that associated with failure without intracardiac shunt.

Clinical Features Other than Cyanosis—Reports on physical examinations in cases of ventricular septal defect confirmed the frequency of loud, rough systolic murmurs best heard at the lower left sternal border. This Roger murmur occurred frequently enough to be considered pathognomonic for this syndrome. The often quoted statement that the intensity of such murmurs varies inversely with the size of the defect is not confirmed in this series, because the few instances

of soft murmurs or of absent murmurs were found not only with large defects but were scattered irregularly among the cases of various sizes of defects. In addition, the fact that loud systolic murmurs were present in all cases of complete absence of the ventricular septum speaks against the theory of inverse relationship between the size of the defect and the intensity of the murmur. The fact that in some cases murmurs were reported in other locations than that of the typical Roger murmur is not surprising, since commoner and better known murmurs, such as the one associated with aortic stenosis, also show frequent deviation from the "typical" location. In the rare cases in which mention was made of the transmission of murmurs, no regularity could be noted as to the direction of the transmission. Early diastolic blowing murmurs at the left sternal border were commonly noted, but it is not clear whether they originated in the defect or were due to relative pulmonary insufficiency. In cases in which large, pulsating pulmonary vessels are noted, the second possibility is more appealing.

Relatively few reports on roentgenographic examinations were available. Judging from those and from the appearance of the pathologic specimens, it seems logical to expect normal or insignificantly enlarged cardiac shadows in cases with smaller defects of the ventricular septum. In the presence of a large defect, the cardiac silhouette acquires the characteristic shape associated with overloading of the pulmonary circulation, such as occurs with large defects of the atrial septum or in the Eisenmenger complex, namely, enlargement of the heart with particular prominence of the conus arteriosus and the pulmonary artery and its branches, with pulsating hilar shadows and pulmonary congestion.

The electrocardiogram may be normal or may show preponderance of the right ventricle of various degrees, but apparently the most characteristic pattern for this syndrome is the presence of tall and diphasic QRS complexes in the conventional leads, with or without prolongation. This pattern is also noted in the case of the trilocular heart with a single ventricle, a relationship to the absence of a portion or all of the ventricular septum is therefore indicated. It should be noted, however, that intraventricular conduction defects occurring in congenital heart disease are not limited to lesions associated with defects in the ventricular septum. They were observed in cases of pulmonary stenosis with an intact ventricular septum.¹⁹

Prognosis—The prognostic evaluation of a congenital malformation of the heart depends on two factors—the effect of structural abnormality on the circulation and the susceptibility to complicating infections. The first factor is the predictable one. Failure of the circu-

19 Selzer, A., Carnes, W. H., Noble, C. A., Higgins, W. H., and Holmes, R. O. The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale. *Am J Med* 63, 1949.

lation occurs after years of stress and strain on the heart, which can be detected by the usual clinical methods, such as estimating the cardiac size, the size of the pulmonary vessels and the electrocardiographic evidence of ventricular strain. In the case of defect of the ventricular septum, patients showing evidence of a large interventricular fistula can be placed in the same category as those with large defects of the atrial septum and sizable ductus arteriosus. The lesions are not serious enough to interfere with growth and survival to adult life but reduce the life expectancy to a considerable degree, allowing only an occasional patient to survive beyond early middle age.

The hazard of bacterial infection applies in all cases, regardless of the size of the defect or of its effect on the circulatory dynamics. This susceptibility to subacute bacterial endocarditis is high. In this series, 28 per cent of the patients over 1 year of age died of this complication. The susceptibility to cerebral abscess is considerably less than that to bacterial endocarditis. The incidence of pulmonary tuberculosis was small in this series, and its occurrence was probably coincidental.

One is justified in concluding that the conventional concept of defect of the ventricular septum is not entirely correct, as it applies only to small defects. In these cases, moreover, the favorable prognosis is marred by a high susceptibility to bacterial endocarditis, the prevention of which should be the primary objective in the management of patients in this group.

With the increase in the size of ventricular septal defects, it becomes evident that the right side of the heart and the pulmonary circulation are profoundly affected by this malformation.

The diagnosis of congenital heart disease has been facilitated in recent years by the introduction of new methods, such as angiocardiology and venous catheterization of the heart. The first of these methods seems to be of little value in diagnosing a defect with a left to right intracardiac shunt. Venous catheterization of the heart, on the other hand, may demonstrate such a shunt if a highly oxygenated blood sample is obtained from the right ventricle. Proof of the infallibility of the newer method, however, will have to await correlation of the findings with the results of autopsy in a considerable series of cases.

SUMMARY AND CONCLUSIONS

Twelve cases of uncomplicated ventricular septal defect in which autopsy was performed are reported, and the clinical and pathologic findings in these and in 80 other cases in the literature are presented.

1. Taussig's division of defects of the ventricular septum into "simple" and "high" categories as clinical entities is not confirmed. In the vast majority of ventricular septal defects of all sizes there is a typical interventricular foramen, located in and anterior to the mem-

branous septum, connecting the area of the left ventricle immediately underneath the aortic valves with that of the right ventricle in front of the median leaflet of the tricuspid valve. Only in rare instances are defects of the lower portion of the septum located in the muscular part, and these present no distinctive clinical features.

2 It is suggested, in accordance with Spitzer's theory, that the typical interventricular foramen is related to the same process of maldevelopment which in severer forms causes the Eisenmenger complex, the tetralogy of Fallot and transposition of the arterial trunks. For that reason, the dividing line between the larger types of uncomplicated defect of the ventricular septum and the Eisenmenger complex is indistinct and all degrees of transitional forms can be found.

3 Cyanosis is absent from cases of uncomplicated defect of the ventricular septum. It is believed that any significant decrease in oxygen saturation in the arterial blood is due to congenital or acquired overriding of the aorta, and that cases in which this is found should be classified as instances of the Eisenmenger complex. It is suggested that the presence of cyanosis may be a more reliable factor in differentiating the two syndromes than the appearance of the pathologic specimen, since reconstruction of the aortic orifice in its proper relation to the defect during life may be difficult.

4 The effect of defect of the ventricular septum on the circulation is related to the size of the communication. Smaller defects may have no effect on circulatory dynamics, whereas larger ones almost always lead to considerable overloading of the pulmonary circulation with dilatation of the pulmonary artery and hypertrophy, strain and failure of the right ventricle.

5 The characteristic "Roger murmur," the rough and loud systolic murmur at the lower left sternal border, was observed fairly consistently in this series and can be considered pathognomonic for defect of the ventricular septum. Occasionally, however, systolic murmurs were located in other points of the chest wall or were soft or even absent. There was no apparent relation between the intensity of the murmur and the size of the defect, and loud systolic murmurs were heard in cases of complete absence of the ventricular septum. Early diastolic blowing murmurs at the left sternal border were common.

6 The roentgenologic appearance of the cardiac shadow varied from a normal cardiac silhouette to cardiac enlargement with prominence of the shadow of the pulmonary artery and that of its branches. In large defects, the configuration resembled that usually associated with defects of the atrial septum or the Eisenmenger complex.

7 Electrocardiographic findings also were variable, but in some cases intraventricular conduction defects with very tall diphasic QRS complexes were reported. These findings were also reported in cases with complete absence of the ventricular septum.

8 The prognosis in defect of the ventricular septum is favorable in milder cases and guarded in cases with large shunts. In all cases there is a relatively high susceptibility to bacterial infection of the endocardium, which accounted for 22 per cent of the deaths in this series.

PHYTOBEZOAR IN THE GASTRIC STUMP

Report of a Case and Discussion of Therapy

L WALK, M D
ESKILSTUNA, SWEDEN

ALTHOUGH there are 170 cases of phytobezoar to be found in the literature at the time of this report, the concretion apparently has never before been observed in the stump of a partially resected stomach

REPORT OF CASE

An unmarried woman of 69 for many years had epigastric soreness after meals. During the past year deterioration, a 25 Kg loss of weight, vomiting and occasional moderate episodes of diarrhea had occurred. For three months, the patient had usually been confined to bed. On admission to the surgical department (May 21) because of a suspected malignant growth in the antrum, the red blood cell count was 1,500,000 with 48 per cent hemoglobin and 2,100 leukocytes. The patient showed considerable weakness. The temperature rose to 38.5 C (101.3 F). After four blood transfusions, the hemoglobin rose to 82 per cent with 3,700,000 erythrocytes, the temperature gradually subsided and high resection of the stomach was carried out (June 6). There was anacidity before as well as after the operation, and mucosal atrophy and chronic gastritis were noted in the resected specimen.

Soon after the operation, frequent vomiting developed, necessitating prolonged clinical treatment. No relation of the vomiting to meals was noted. Roentgenologically (July 18) the anastomosis was found to be very narrow, the gastric stump containing intermediary fluid. On August 4, the fluid had diminished somewhat. Five days later, however, a new roentgenoscopic examination was requested because of increased vomiting and epigastric pains. At that time (August 9), the stomach contained a coagulum 5 by 6 by 7.5 cm (figure). Roentgen exploration on August 15 and 25 and on September 6 and 19 showed the coagulum to be gradually decreasing in size, and it was no more to be demonstrated on September 23. Retention of food particles, however, was observed on November 14. Because of the persistent vomiting and loss of weight, a new operation was performed on December 9. The anastomosis was found to be only 4 mm in diameter. A new opening of 2 cm was made.

REVIEW OF LITERATURE

The spontaneous disappearance of a phytobezoar (table 1) seems to be more frequent than would appear from the literature, in 9 recorded cases, it has been complete in 7. The longest estimated duration followed by complete disappearance has thus far been four weeks.

From the Roentgen Department (Head O Sandstrom, M D) and the Surgical Department (Head H Wahren, M D), Central Hospital

I published a report of a case in which healing was spontaneous¹ Later I observed 2 similar instances In 1, a man of 50 even had a deep ulcer on the lesser curvature of the stomach, the foreign body disappeared in a week In the other, in a middle-aged woman, it disappeared in some days These observations indicate our lack of knowledge as to the number of spontaneous healings The foreign bodies described in table 1 were composed of diverse vegetable materials, the percentage of persimmon balls was low in this series, although 70 per cent of all phytobezoars recorded in the literature have been composed of persimmons A persimmon bezoar, once formed, seems to have special resistance

Most phytobezoars have been removed surgically as soon as the diagnosis was established Operation is indicated in long-standing



Phytobezoar in the gastric stump, showing progressive diminution in size A, three days, B, nine days, and C, nineteen days after onset of symptoms

cases especially in those in which persimmon balls or cellulose fibers, evidently resistant to digestion, made up the mass On 17 occasions, however the operation was performed during the first four weeks of the disease, that period being the longest time in which spontaneous disappearance has been noted (table 2), in 14 of these cases in which the outcome was stated it was favorable Probably in some of them there would have been spontaneous disappearance If a case is of less than four weeks' duration, it seems advisable to wait, apparently this has not been pointed out before Provided the diagnosis has been secured and no complications demand immediate removal, the patient should be observed in the clinic For the important differential diag-

¹ Walk, L. Gastroskopisch untersuchter Fall von Phytobezoar aus Beeren von *Crataegus*, Klin Wchnschr 19 894-895, 1940

TABLE 1—*Summary of the Literature of Spontaneous Disappearance of Phytobezoar*

Author	Composition of Bezoar	Sex	Age	Duration of Bezoar before Hospitalization	Length of Hospitalization	Comment
Capelle (1861)	Vegetable debris containing calcareous substances	F	43	Epigastric tumor observed 4 weeks	Not hospitalized	Phytobezoar 9 cm in circumference vomited after colocynth and mild mercurous chloride, disappearance of palpable tumor, and gradual subsidence of complaints, recovery (patient observed 5 years)
King (1894)	Persimmons	M	14	Unknown	2 weeks	Natural voiding after massage of tumor after 2 2 weeks' treatment
Hichens and Odgers (1912)	Coconut fibers	F	24	3 months		Incomplete spontaneous passage (2 masses after 3 months, the rest later removed at operation)
Hart (1923) case 8	Prune and raisin skins	F	Middle-aged	Unknown	Some days	Achylia, spontaneous passage after administration of hydrochloric acid
DeBakey and Ochsner (1938-1939) case 6	Persimmons	M	37	Several months	14 days	Incomplete passage (another phytobezoar in stomach?)
Lawrie (1939)	Persimmons	M	23	9 days	22 days	Palpable mass rapidly diminished in size and finally disappeared after daily gastric lavage and massage
Walk (1941)	Hawthorne berries	F	57	4 weeks	Some days	Spontaneous passage after ulcer regimen, belladonna and magnesium oxide, complete recovery (patient observed 3 years)
Cambel and Konuralp (1943) case 1	Not stated	M	55	Unknown	Not stated	Phytobezoars (55 to 75 Gm) vomited at gastric lavage by patients with stenosing cancer of the stomach
case 2	Not stated	M	46	Unknown	Not stated	

TABLE 2—*Cases of Uncomplicated Phytobezoar, Operated on During the First Four Weeks of the Disease*

Author	Composition of Bezoar	Sex	Age	Duration of Bezoar Before Admission	Hospitalized Before Operation	Comment
Hart (1923) case 4	Persimmons	F	40	Some days	Not stated	Total duration of disease 7 days, no preoperative diagnosis
Hibi (1927) case 1	Persimmons	F	3	5 days	Not stated	Hospitalized for 22 days
Potter (1930)	Persimmons	M	57	3 weeks	6 days	Gastric ulcer
Castellani (1931)	Diospyros lotus	M	9	15 days	Some days	
Zaccaria (1931) case 3	Persimmons		8	20 days?	Not stated	Gastralgia during some months, loss of appetite, sometimes vomiting
Wyatt (1932)	Persimmons	F	52	4 days	Not stated	Three masses
Zanetti (1933)	Grape skins		14	8 days	Not stated	
Owen (1933) case 1	Persimmons	M	35	3 weeks		
Henschen (1933)	Persimmons	F	6	2 3 weeks	Not stated	Palpable epigastric tumor, no roentgen examination
Murdock (1934) case 2	Persimmons	M	4	2 days		Operated immediately Two masses
Case 8	Persimmons	F	61	6 days	4 days	
Baur (1936)	Plant fibers (plums) and gummy substance	F	30	15 days	Not stated	Very small phytobezoar of the size of a filbert
Rutledge (1937)	Persimmons	M	24	10 days	3 days	Great prepyloric ulcer
White (1938) case 1	Persimmons	M	48	15 days	Not stated	2 similar attacks before onset of present illness (spontaneous passing of persimmon balls in some days?)
Woolsey (1938)	Persimmons	M	9	10 days	Not stated	
Gürkan (1943)	Not stated	F	50	25 days	Not stated	Slight gastric distress and loss of weight during some years
Peronato (1941) case 1	Diospyros lotus	F	8	20 days	1 day	Pasty, soft mass weighing 235 Gm

nosis, gastroscopy has been valuable² Repeated roentgenologic examinations, as in the present case, have apparently not been reported The rapid diminution in size of a phytobezoar of short duration is probably important, by means of palpation even a persimmon bezoar has been observed to disappear spontaneously³ (table 1) On the contrary, slight diminution in size in a case of long standing seems to lack prognostic value, it has been noted in 2 cases, in 1 roentgenoscopically and in the other by palpation In the first of these,⁴ two roentgenoscopic examinations were made with an interval of two months between them, operation had to be done In the other,⁵ an undiagnosed phytobezoar, although it diminished slightly to palpation, led to cachexia and, finally, to death

The differentiation of phytobezoars formed of interlacing plant fibers from those composed of coagulated organic substance⁶ has not been tested as to its clinical value Dietetic treatment as for peptic ulcer, combined with the administration of antacid and antispasmodic drugs, has been used during hospitalization¹, in the presence of achylia, hydrochloric acid has been administered⁷ In most cases of phytobezoar in which the gastric juice has been examined, free acid has been demonstrated and high acidity has been frequent Anacidity has been observed in 4 cases only⁸ In my case, there was anacidity, and histologically mucosal atrophy and gastritis were observed Gastric ulcer, frequent in phytobezoar, was not to be demonstrated The usual

2 (a) Walk¹ (b) Moersch, H J, and Walters, W Phytobezoar with Visualization by Means of Gastroscopy, *Am J Digest Dis* **3**:15-17, 1936 Ruffin, J M, and Reeves, R J The Value of Gastroscopy in the Diagnosis of Phytobezoar, *ibid* **5** 745-746, 1939 (c) Browne, D C, and McHardy, G Gastroscopy and Phytobezoar Report of Case of Diospyrobezoar, *Arch Int Med* **65** 368-374 (Feb) 1940 (d) Patterson, C O, and Rouse, M O Foreign Bodies in the Stomach Observed Through the Gastroscope, *Texas State J Med* **36** 238-242, 1940 (e) Cohn, A L, and White, A S Gastroscopic Diagnosis of Phytobezoar, *Am J Surg* **51** 432-435, 1941

3 Lawrie, E S A Case of Persimmon Bezoar, *J Malaya Br, Brit M A* **3** 190-193, 1939

4 McCarley, T H, and Greenberger, E D Persimmon Phytobezoar Mistaken for Gastric Cancer, *Radiology* **36** 232-233, 1941

5 Kooyker, H A Zur Casuistik der Gastrolithen beim Menschen, *Ztschr klin Med* **14** 203-211, 1888

6 Izumi, S, Isida, K, and Iwamoto, M The Mechanism of Formation of Phytobezoars, with Special Reference to Persimmon Ball, *Jap J M Sc Tr, II, Biochem* **2** 21-35, 1933

7 Hart, W E Phytobezoars, *J A M A* **81** 1870-1875 (Dec 1) 1923

8 (a) Hart⁷ (b) Crossan, E T Phytobezoar with Gastric Ulcer, *Ann Surg* **101** 1451-1452, 1935 (c) Chont, L K Phytobezoar and Its Formation in Vitro, *Radiology* **38** 14-21, 1942

symptom complex was noted even in this case, although there were symptoms also of postoperative stenosis, complicating the clinical findings

Although there are reports in the literature of 4 cases in which a phytobezoar apparently came from a stomach, which had been operated on, the foreign body has never been directly observed at this site. On 1 occasion,⁹ the stomach had been partially resected according to the method of Reichel and Polya because of a phytobezoar of five weeks duration, associated with two gastric ulcers. Nine months later, obstruction developed high in the intestine, and another bezoar 6.5 by 8 cm and weighing 120 Gm—apparently newly formed in the resected stomach but perhaps only a part of a double bezoar overlooked at the first operation—had to be removed from the jejunum, 3 inches (7.5 cm) distal to the anastomosis. In another case,¹⁰ obstruction of the jejunum by a persimmon ball was observed, three months before, pyloric resection and end to end anastomosis with the duodenum had been performed because of the presence of an ulcer and the suspicion of malignancy, but apparently the foreign body had been overlooked and left in the stomach at the first operation. In the third case,⁷ the patient had a gastroenterostomy and was operated on for intestinal obstruction, a cylindrical foreign body 5 by 7.5 cm was removed from the jejunum, a few inches from the anastomosis. Even in the fourth case,¹¹ in which the patient had a gastroenterostomy, a phytobezoar 12 cm in diameter and weighing 126 Gm was removed from the intestine, 1 mm distal to the anastomosis. All 4 patients recovered. Artificial anastomoses seem to favor the passage of especially voluminous masses, which regularly become fixed in the upper portion of the jejunum, the postoperative results in this complication, however, have been good. Except in cases in which the anastomosis is very narrow, a phytobezoar in a stomach which has been operated on should be removed surgically without much delay. As for the present case with a stenotic anastomosis, expectation was correct. In the stomach which has not been operated on, on the contrary, if a phytobezoar passes the pylorus and becomes fixed, it is usually in the distal portion of the ileum, in 34 cases, only 7 exceptions were noted, the foreign body being fixed

9 Binotto, A. Contributo allo studio dei corpi estranei del canale gastroenterico, *Gior veneto di sc med* **13** 445-462, 1939

10 Bullock, W. O., in discussion on Griffith, F. W. Obstruction of Small Intestine Due to Food Products, *Ann Surg* **103** 769-772, 1936

11 Peronato, G. Fitobezoar dello stomaco, del tenue, del colon, *Arch ital di chir* **61** 174-194, 1941 (bibliography)

in the duodenum¹² or the jejunum¹³ In cases in which the stomach has not been operated on, the obstructions caused by *Diospyros virginiana* have occurred in the ileum close to the cecum, whereas those caused by the Japanese variety of the same plant (in whatever part of the world) have been in the upper portion of the small intestine, from the duodenum to the jejunum, apparently the size of a bezoar is not the only factor determining the site of an obstruction¹⁴

The case material on phytobezoar shows no arguments against clinical expectation in suitable cases (Agglomerations of vegetable material in the stomach have been called phytobezoars without account for the duration No well defined criteria exist as to those removed from the intestine A great number of agglomerations leave the stomach some hours or days after being formed, usually during the first hours, these have been called "food boli" in the literature Others enter the intestine not before some weeks, months or years after ingestion When a long time passes between ingestion and intestinal obstruction, the case is usually recorded as one of phytobezoar Two cases were listed as cases of phytobezoar by some authors,¹⁵ and as cases of food boli, by others¹⁶ Unchewed masses of ingesta¹⁷ should be differentiated from real phytobezoars and food boli) Except for an undiagnosed case of the preoerogenous period, a complication has developed in a hospital in only 2 cases In the first, intestinal obstruction and peritonitis developed in a patient hospitalized after childbirth, she recovered after the removal of a foreign body 2 cm in diameter from the intestine at the site of an old adhesion¹⁸ In the second, ileus of four days' duration was followed by spontaneous recovery and passing of a phytobezoar in a child operated on for another intestinal obstruction by a bezoar fourteen days before¹⁹

12 (a) Izumi, Isida and Iwamoto⁶ (b) Langenbuch Demonstration eigenthümlich grosser Concretionen des Magens und des Dunndarms, welche durch Enterotomie herausgefordert worden sind, Verhandl d deutsch Gesellsch f Chir **9** 54, 1881 Yeo, G, cited by Peronato¹¹

13 (a) Izumi, Isida and Iwamoto⁶ (b) Lobinger, A S, cited by Hargrave, R L, and Hargrave, R Acute Intestinal Obstruction by Persimmon Phytobezoar, Report of Two Cases, Ann Surg **104** 65-73, 1936 (c) Newburger¹⁴

14 Newburger, B Intestinal Obstruction Due to Phytobezoar, Rev Gastroenterol **8** 293-300, 1941 (bibliography)

15 Lobinger^{13b} Simpson, B S Intestinal Obstruction by Unusual Form of Enterolith, Edinburgh M J **30** 176-178, 1923

16 (a) Caylor, H D, and Nickel, A C Intestinal Obstruction from Food Bolus, Ann Surg **104** 151-154, 1936 (b) Elliot, A H Intestinal Obstruction Caused by Food, Am J M Sc **184** 85-94, 1932

17 Obstruction of Small Intestine, Cabot Case 28212, New England J Med **226** 864-866, 1942

18 Downing, W Obstruction and Perforation of Small Intestine Due to Coprolith, J A M A **86** 550 (Feb 20) 1926

19 Hibi, H Phytobezoar, Nippon Shokakibyo Gakkai Zasshi **26** 27-32, 1927

Since one must be prepared to meet complications an analysis of the literature on their occurrence and therapy is important. There is evidence of a number of unreported instances of the spontaneous disappearance of a phytobezoar, the literature probably gives a one-sided view. A notion of the frequency of disappearance may be obtained from table 3, which contains data on the cases of food bolus in the literature²⁰ for comparison. The material up to 1938 has previously been collected^{20c}, references not given in the present article are to be found in that bibliography. Reports on 44 additional cases have appeared in the recent literature²¹. The prognosis is probably generally

TABLE 3—Complications in 130 Cases of Phytobezoar and 28 Cases of Food Bolus*

Time After Ingestion	Uncomplicated Cases (Operated on or Healed Spontaneously)	Intestinal Obstruction and Perforation	Ulcer Perforation	Gastric Bleeding
12 hours		(14)†	1‡	
2 days		1 (9)		
3-7 days	3	5 (3)		
1-2 weeks	5	3 (1)		1
2-4 weeks	14	1	1	
1-2 months	9	1 (1)	2	2
2-3 months	10	2		1
3-6 months	13	2		1
6-12 months	20	5	1	
1-2 years	11	1		
2-5 years	7	2	1	1
5-11 years	2		.	1

* Figures in parentheses represent the number of cases of food bolus

† In 1 case the food bolus measuring 1½ by 2½ inches (3 by 6 cm) was vomited

‡ This was a case of gastric rupture in child aged 3 years

20 (a) Caylor and Nickel^{10a} (b) Elliot^{10b} (c) DeBakey, M, and Ochsner, A. Bezoars and Concretions, *Surgery* **4** 934-963, 1938, **5** 132-160, 1939 (bibliography) (d) Latchmore, A. J. C. Stomach-Ache, *Lancet* **1** 1153-1155, 1940

21 (a) Walk¹ (b) Footnotes 2, b, c, d and e, 3 and 4 (c) Chont^{8c} (d) Binotto⁹ (e) Peronato¹¹ (f) Newburger¹⁴ (g) Bernardes de Oliveira, A. Dois casos raros de cirurgia gástrica: fitobezoar, adenoma do estômago, *Rev de cir de São Paulo* **7** 197-222, 1941 (h) Cambel, P, and Konuralp, H. Z. Ueber Hortobezoare in der Türkei und zwei eigene Fälle bei Magenkarzinom, *Zentralbl allg Path u path Anat* **80** 245-248, 1943 (i) Cavusoglu, E, cited by Cambel and Konuralp^{21h} (j) Gurkan, K. J. Phytobezoar-Fall mit interessantem radioskopischem Befund, *Chirurg* **15** 554-555, 1943 (k) Hancock, J. C. Japanese Perissimon Bezoars, *J Iowa M Soc* **28** 234-238, 1938 (l) Hirsch, D. J, cited by Groves in discussion on White^{21v} (m) Hoge, A. F. Phytobezoar, *J Arkansas M Soc* **39** 157-159, 1942 (n) Lyons, C. G, and Cody, G. L. Bezoar, *Radiology* **31** 225-239, 1938 (o) Maes, U, in discussion on White^{21v} (p)

better than might appear from the following analysis of the literature, which contains reports even on patients admitted for treatment late and in poor condition

Intestinal Obstruction—This has most frequently developed during the first twelve hours and in a great number of cases during the first two days after ingestion. The risk of this complication has diminished on the third day. It is slight but still present after the second week, and obstruction has even occurred two years after ingestion.

The literature on this complication was recently summarized¹⁴. The mortality of 40 per cent can probably be considerably reduced if the complication should develop while the patient is being treated in the clinic and is treated in good time. Roentgen examination in case of an acute abdominal condition, hitherto used in 2 cases,²² permits a better diagnosis than do clinical symptoms only. Even in cases of spontaneous passing of a phytobezoar there may be temporary signs of intestinal obstruction²³. An obstruction may be incomplete²⁴ but followed by ulceration of the intestinal wall and perforation^{24b}. The foreign body may remain in the intestine, clinically resembling a tumor²⁵ or an appendical abscess²⁶. At operation for an intestinal obstruction even the stomach should be palpated, another bezoar was thus detected in the stomach in some cases²⁷ and in others was overlooked there²⁸.

Gastric Ulcer, Perforation and Hemorrhage—Gastric ulcer has been recorded in 39 cases of phytobezoar. Its presence apparently does not alter the therapy as far as it concerns the foreign body.

McNeill, J. H. Persimmon Phytobezoar with Case Report, *Ann Int Med* **14** 2412-2417, 1941. (q) Parzani, C. Sui corpi liberi della cavita gastrica, *Gior veneto di sc med* **12** 32-36, 1938. (r) Rachlin, S. A. Intra-gastric Benign Tumor Associated with Penetrating Ulcer of Lesser Curvature, *M Bull Vet Admin* **19** 113-114, 1942. (s) Ramstad, N. O. Phytobezoar with Gastric Ulcer, *Journal-Lancet* **58** 505-506, 1938. (t) Serck-Hansen, T. Phytobezoar, *Med rev*, Bergen **55** 171-174, 1938. (u) Snelling, J. G., cited by Graves, in discussion on White^{21v}. (v) White, R. J., Persimmon Phytobezoar, *South M J* **31** 750-756 1938. (w) Woolsey, R. A., in discussion on White^{21v}.

22 Newburger¹⁴. De Bakey and Ochsner^{20c}.

23 (a) Hibi¹⁹. (b) DeBakey and Ochsner^{20c}. (c) Hichens, P. S., and Odgers, N. B. A Case of Vegetable Gastrolith, *Brit M J* **1** 606-607, 1912.

24 (a) Cited by Newburger¹⁴. (b) Tosatti, cited by Peronato¹¹.

25 Lagoutte, cited by Peronato¹¹.

26 Murdock, H. D. Persimmon Bezoars Occurring Around Tulsa, Oklahoma, *J Oklahoma M A* **27** 442-447, 1934.

27 Hart⁷. Langenbuch^{12b}. Murdock²⁶. Balfour, D. C., and Good, R. W. Phytobezoar Associated with Gastric Ulcer, *Am J Surg* **6** 579-587, 1929. Good, R. W. Phytobezoar, *Proc Staff Meet*, Mayo Clin **3** 237, 1928.

28 Moersch and Walters^{2b}. Hibi¹⁹. DeBakey and Ochsner^{20c}. Hirsch²¹ⁱ. Maes^{21o}.

The question arises as to the most rational handling of an ulcer in a patient operated on for phytobezoar. In 4 cases²⁹ partial resection of the stomach was carried out, in 2, excision of the ulcer,³⁰ and in 2, gastroenterostomy⁸, in an additional case, the ulcer was slightly cauter-

TABLE 4—Late Results in Cases of Phytobezoar Associated with Gastric Ulcer

Author	Duration of Observation	Sex	Age	Gastric Symptoms Before Bezoar	Therapy	Ulcer	Results
Smith (1933) case 2	27 mo	M	53	Chronic cholecystitis and disease of appendix	Operation	Large ulcer on lesser curvature penetrating into pancreas, in operable	Dull pain at umbilical level not relieved by food or alkalis, roentgenograms showed no ulcer, considered chronic cholecystitis
Crossan (1935)	3 mo	M	42	None	Operation	Saddle ulcers on lesser curvature, each 2 cm in diameter	Well except for a few attacks of nausea
Moersch and Walters (1936)	4 mo	M	49	None	Operation	Small healed ulcer on lesser curvature	Free of all symptoms after operation
Rutledge (1937)	4 mo	M	24	None	Operation	Large penetrating prepyloric ulcer	Free of gastric symptoms
Satterfield (1937)	4 mo	M	53	Appeared 13 years previously, recovered	Operation	3 prepyloric ulcers, the largest 4 by 4 cm	No digestive symptoms
Allen (1938) case 1	9 mo	M	71	Ulcer ante dating phytobezoar?	Operation (twice)	Scar at pylorus, no ulcer at second operation	Good health reported
DeBailey and Ochsner (1938) case 7	Not stated	M	59	None	Operation	On greater curvature 2.5 cm in diameter	Completely relieved of all complaints, roentgenograms showed no ulcer
White (1938) case 1	10 mo	M	48		Operation	1.5 cm in diameter 7.5 cm above pylorus	Gastric trouble 6 weeks postoperatively, recovered, perfectly well (table 2)
White (1938) case 2	9 mo	M	46		Operation, cauterization	Fresh ulcer on lesser curvature	Recovered, perfectly well ever since
Ramstad (1938)	2½ mo	F	38	Operation for gallstones	Operation	2 cm in diameter involving only the mucosa	No gastric distress, roentgenograms showed no ulcer
Walk (1940)	3 yr	F	57	None	Conservative	0.5 cm in diameter at angulus	Complete recovery after spontaneous disappearance of bezoar (table 1)
McNeill (1941)	1 yr	M	57		Excision of ulcer	1 by 2 cm on greater curvature	No complaints after operation
Hoge (1942)	3 mo	M	61	Ulcer ante dating bezoar	Resection	2 cm in diameter deep in middle part of stomach	No more symptoms

ized^{21v} All the patients recovered. In 21 cases the ulcer was left untouched at operation. This group apparently included even patients

29 Binotto⁹ Hoge^{21m} Balfour, D. C., and Good, R. W. Phytobezoar Associated with Gastric Ulcer, *Am J Surg* 6:579-587, 1929. Good, R. W. Phytobezoar, *Proc Staff Meet, Mayo Clin* 3:237, 1928.

30 (a) McNeill^{21p} (b) Potter, R. P. Phytobezoar, *Radiology* 15:685-688, 1930.

in poor condition. There were 3 deaths from pneumonia³¹ and 1 from peritonitis³². Late results have been recorded in 13 cases in the literature (table 4). They were good, even large ulcers can thus safely be left untouched at the gastrotomy for removal of the foreign body. The opinion that most gastric ulcers in phytobezoar are decubital is thus supported by the late results, which apparently have not been analyzed before. When the results are compared with those in 11 cases without ulcer,³³ the difference is less than might be expected. In this group, occasional residual sensations of gastric distress were noted on one occasion.⁷ Partial resection of the stomach is thus indicated only when the ulcer has been present and resistant to therapy before the appearance of the bezoar or when special morphologic features (fixation to extragastric organs, penetration to the liver or pancreas or risk of stenosis) demand radical surgical measures. Independent ulcer, not caused by the bezoar, has probably been observed in the duodenum as well as in the stomach.³⁴ When an operation is performed for phytobezoar, an independent ulcer probably can be handled as in cases of ordinary ulcer, without the special conservatism needed in the therapy of decubitus ulcer.

Perforation has occurred in cases of gastroduodenal ulcer without periods of predilection (table 3). In 1 case there was a duodenal ulcer^{34b} and in the remaining 5 a gastric ulcer located in the prepyloric area,^{34b} 6 cm proximal to the pylorus^{8c} or on the lesser curvature, the exact site not being stated.³⁵ No perforation has hitherto been observed in ulcer of the greater curvature.³⁶ In the surgical cases³⁷ the mortality from peritonitis was 40 per cent. Acute perforation of the

31 Brown and McHardy^{2c} Chont^{8c}

32 David, V. C. Pseudocarcinoma of the Stomach, *Ann Surg* **87** 555-565, 1928

33 (a) Patterson and Rouse^{2d} (b) Lawrie³ (c) Hart⁷ (d) Hancock^{21k} (e) Smith, L. A. Hematemesis from Phytobezoar, *Am J Surg* **22** 565-567, 1933 (f) Capelle. Concrétion gastrique, *J med de Brux*, 1861, p 147 (g) Garrett, D. L. Phytobezoar *Diospyri Virginianae*. Case Report, *J Oklahoma M A* **21** 64, 1928 (h) Porter, W. B., and McKinney, J. T. Phytobezoar *Diospyri Virginianae*, *Am J M Sc* **72** 703-706, 1926 (i) Wyatt, W. S. Phytobezoar, *Kentucky M J* **30** 79-80, 1932 (j) Thorek, P., and Rutter, C. Trichobezoar and Phytobezoar, *Am J Surg* **35** 603-606, 1937

34 (a) Hart⁷ (b) Allen, L. G. Phytobezoar, *Am J Roentgenol* **39** 67-74, 1938

35 Chont^{8c} Murdock²⁶

36 DeBakey and Ochsner^{20c} McNeill^{21p}

37 Chont^{8c} Murdock²⁶ Allen^{34b}

anterior wall of the stomach during the first twelve hours after ingestion was noted in a child of 3 years ³⁸

Gastric hemorrhage occurred in 7 cases of various durations (table 3) Sometimes slight,^{2e} on other occasions it caused anemia,³⁹ and hemoglobin values of 30 to 41 per cent were recorded ⁴⁰ The treatment has been conservative Operated on as soon as the general condition improved, 6 patients recovered ⁴¹, on 1 occasion death from bronchopneumonia and pleural effusion occurred ^{8c}

Emaciation—Emaciation, with or without anemia, has been observed in long-standing cases ⁴², it has even developed in one or two months ⁴³ and has sometimes been associated with dehydration ⁴⁴, in cases in which operation has been performed after clinical treatment, which in some cases has lasted for twenty-six days, all patients have recovered The results have thus been favorable Grave emaciation, finally leading to death, has been observed in an undiagnosed case of the preroentgen period ⁵

For comparison, the mortality in 46 uncomplicated cases of phytobezoar in the stomach in which operation was performed was 4.3 per cent ⁴⁵

SUMMARY

A unique case of phytobezoar in the stump after resection of the stomach is reported

Not infrequently a phytobezoar disappears spontaneously If its duration in a stomach not operated on does not exceed four weeks and if no complications demand immediate surgical intervention, the patient should be observed in the clinic and the operation postponed The therapy of phytobezoar in a stomach on which operation has been done (with a gastroenterostomy or resection anastomosis) is different

38 Herzog, M A A Peculiar Gastrolith Leading to Perforation and Death, *Tr Chicago Path Soc* 4 162-164, 1899-1901

39 (a) Patterson and Rouse ^{2d} (b) McCarley and Greenberger ⁴ (c) Chont ^{8c} (d) DeBakey and Ochsner ^{20c} (e) Smith ^{33e} (f) Satterfield, W T Phytobezoar, *Memphis M J* 12 140-143, 1937

40 Patterson and Rouse ^{2d} McCarley and Greenberger ⁴ Chont ^{8c}

41 Patterson and Rouse ^{2d} McCarley and Greenberger ⁴ DeBakey and Ochsner ^{20c} Smith ^{33e} Satterfield ^{39f}

42 Chont ^{8c} Hamdi, H Drei Horto- oder Phytobezoarfälle beim Menschen, *Deutsche med Wchnschr* 52 2122-2123, 1926

43 Patterson and Rouse ^{2d} Murdock ²⁶

44 Rodgers, F D Phytobezoar of Persimmon Origin, *Radiology* 29 494-498, 1937

45 Hart ⁷ Outten, W B Case of Double Gastrolith Removed by Gastro-
tomy, *M Fortnightly* 6 445-452, 1894

A phytobezoar in such a stomach should be removed surgically without much delay because of the great risk of obstruction high in the intestine. Expectation of spontaneous disappearance is here justified only if the anastomosis is very narrow. As far as I know, this fact has not been pointed out in the literature.

Late results in cases of phytobezoar show remarkably good healing of a gastric ulcer after the disappearance or removal of the foreign body. Even a large ulcer can thus be left untouched at the operation for removal of the foreign body. Only when an ulcer is evidently independent of the bezoar, as observed on rare occasions, is the indication for gastric resection the same as for ordinary ulcer.

News and Comment

THIRD ANNUAL CLINICAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The Third Annual Clinical Session of the American Medical Association will be held in Washington, D C, December 6 to 9

The Clinical Session will provide a full scale scientific program specifically designed for the general practitioner Outstanding physicians will discuss such subjects as diabetes, pediatrics, laboratory diagnosis, physical medicine and rehabilitation, arthritis, dermatology, roentgen ray diagnosis, cancer and poliomyelitis Coordinated with this outstanding scientific program will be approximately one hundred scientific exhibits which will present original work on the subjects discussed

The newest offerings of one hundred and twenty-five manufacturing firms will comprise the Technical Exhibition Here will be found the latest developments in scientific medical research, drugs and equipment

Televised surgical and clinical procedures, similar to those shown in color at the Annual Session of the American Medical Association in Atlantic City last June, will be presented at the Washington meeting The demonstrations will originate in the Johns Hopkins Hospital and will be shown on screens in the Armory The television schedule will be spread over four days

The House of Delegates will meet at the Hotel Statler during this session One of the first orders of business will be the annual selection of the general practitioner who has made an exceptional contribution of service to his community

An entertainment program is being planned for attending physicians and their wives The highlight of this program will be on Wednesday evening, December 7, when the Philip Morris Company will originate its "This Is Your Life" broadcast from the Hotel Statler The radio program will be followed by a stage show, in which outstanding stars will participate

Blanks for hotel reservations and advance registrations may be found in *The Journal of the American Medical Association*

International Symposium on High Altitude Biology—In accordance with a resolution passed by the United Nations Educational, Scientific and Cultural Organization (UNESCO), an International Symposium on High Altitude Biology will take place in Lima, Peru, from Nov 23 to 30, 1949 under the auspices of UNESCO and the government of Peru, the latter having appointed the Executive Committee of the Institute of Andean Biology as organizing committee for the symposium Further information may be obtained from Dr Carlos Monge M, Institute of Andean Biology, Post Office Box 821, Lima, Peru

Urology Award—The American Urological Association offers an annual award of \$1,000 (first prize, \$500, second price, \$300, and third prize, \$200) for essays on the result of clinical or laboratory research in urology Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Washington, D C, May 29 to June 1, 1950

Further information may be secured from the secretary, Dr Charles H de T Shivers, Boardwalk National Arcade Building, Atlantic City, N J Essays must be in his hands before Feb 20, 1950

Chicago Society of Internal Medicine—At the annual meeting of the Chicago Society of Internal Medicine held May 23, 1949, the following officers were elected president, Sidney Strauss, vice president, Howard L Alt, and secretary-treasurer, Ernest G McEwen

Book Reviews

Synopsis of Pediatrics By John Zahorsky, M D, assisted by T S Zahorsky, M D Fifth edition Price, \$5 50 Pp 449 St Louis C V Mosby Company, 1948

Pediatrics includes the growth and development, congenital deformities, all types of trauma and diseases of the young Therefore condensing all pediatric knowledge into one small volume is admittedly a difficult task "Synopsis of Pediatrics" was prepared primarily for medical students and general practitioners Its sixty-two chapters roughly correspond to the sixty hours devoted to didactic pediatrics in the St Louis University School of Medicine The author has spent a long professional life in the practice and teaching of pediatrics The textbook is written from a practical clinical point of view, with major emphasis on office and home diagnosis and treatment Much less emphasis is placed on the more complicated procedures of the hospital and laboratory

The first nine chapters are devoted to feeding, growth and nutrition They represent present day knowledge and opinions prevailing in the pediatric profession Chapters XII to XVIII are devoted to derangements of growth and nutrition Chapters XIX to XXXIII are a condensed practical description of the infectious diseases of childhood with current therapeutic procedures including a discussion of chemotherapy and the antibiotics

The remainder of the text is divided into descriptions of diseases according to anatomic systems and special organs There are six chapters on diseases of the gastrointestinal tract and seven on those of the respiratory organs This properly emphasizes the fact that most diseased conditions encountered in pediatric practice are centered in these organs Five chapters describe functional diseases and pathologic changes of the nervous system The author does not emphasize the psychiatric aspect in proportion to present day pediatric trends Diseases of other systems and special organs such as the genitourinary system, skin, eye and ear are briefly described

In summary, the volume gives a brief but rather comprehensive description of all the common diseases and conditions met in pediatric practice At least some statement is made concerning most of the uncommon and rare pediatric diseases The volume will serve as a textbook for medical students and a handbook for medical men in general

Hemolysis and Related Phenomena By Eric Ponder, M D Price, \$10 Pp 398, with 69 illustrations New York Grune & Stratton, Inc, 1948

Of the 400 pages in this monograph, only a small share are applicable to the clinical problems of the hemolytic diseases The balance is a most thorough presentation of the current status of the unique characteristics of the mammalian erythrocyte The material is presented in a critical and scholarly manner and in great detail It is fascinating for the reviewer—a clinician—to contemplate the amount of research in general physiology devoted to the red cell In his introduction, Dr Ponder says that he has been accused of speaking of the red cell as if it

were a microcosm, an understanding of which would include an understanding of nearly everything else in the cellular world. He points out aptly that "lysis is a special, if somewhat extreme case of altered permeability, the actions of lysins on red cells is a special case of the action of drug-like substances, the osmotic properties of the erythrocyte is a special case of osmotic behavior in general, and so on." He asks, correctly, how we can expect to understand these and other phenomena in complex cells, such as muscle, nerve and gland cells, and he could add neoplastic cells, if we are unable to understand them in the case of the relatively simple, symmetric and inactive erythrocyte. This monograph requires a considerable effort to read, and the general reader may be dismayed by the mathematical formulas and allusions to unfamiliar physical chemical concepts. The presentation, however, is lucid, and the arguments are so well presented that a lack of knowledge of calculus is no bar to an understanding of the material.

The reviewer closed the book with a better appreciation of the complexities of cellular physiology and a greater sympathy for the fundamental scientists who work at the very limits of our present knowledge. The typical complacency of the practical man who feels that he has interpreted a process because he has described it is healthily disturbed by a monograph of this type.

Vitamin A Requirement of Human Adults. An Experimental Study of Vitamin A Deprivation in Man. A Report of the Vitamin A Subcommittee of the Accessory Food Factors Committee. Compiled by E. M. Hume and H. A. Krebs. Medical Research Council Special Report Series, No. 264. Price, 3s. Pp. 145. London: His Majesty's Stationery Office, 1949.

This monograph is a description of a long and complicated experimental study on 23 human volunteers, 16 of whom were given a diet virtually devoid of vitamin A and carotene, the remaining 7 received the same diet with a daily supplement of either 2,500 international units of oleovitamin A U S P (natural vitamin A in oil), or 5,000 international units of carotene. The principal laboratory tests used to determine the extent of vitamin A deficiency were measurements of plasma vitamin A and carotenoid content and various tests of retinal function. The latter were the more reliable. Indisputable evidence of deficiency did not appear until after eight months, ultimately, unmistakable deficiency developed in only 3 of the 16 volunteers who persisted in the tests for twelve to twenty-four months.

Follicular hyperkeratosis, conjunctival degeneration and abnormal fatigue were not encountered. After deficiency states were observed, the amounts of vitamin A or carotene required to treat them were studied. The final conclusion was that 2,500 international units of vitamin A or 7,500 international units of carotene represented the daily requirement for adults. This value is in close agreement with that in the schedule of the National Research Council's Committee on Food and Nutrition.

Carefully conducted studies such as this are extremely useful to the clinician who seeks to evaluate the claims of the vitamin salesmen. The subjects of the experiment were healthy young adults, and it is obvious that similar results would not have been obtained had children, pregnant women or chronically undernourished persons been studied. However, it is good to know how great is the delay before the onset of symptoms of vitamin deficiency. The reserve stores of vitamin A

known to be present in the liver were apparently sufficient to maintain normal retinal function for a period of two hundred to four hundred days. This appears to be a good measure of the adequacy of the average unsupplemented British diet. It is hard to believe that the average American diet is less adequate.

The Rh Blood Groups and Their Clinical Effects By P. L. Mollison, A. E. Mourant and R. R. Race. Medical Research Council Memorandum No. 19. Price, 1s 6d. Pp. 74. London: His Majesty's Stationery Office, 1948.

Just ten years ago, Levine and Stetson discovered an atypical immune agglutinin in the serum of a woman after stillbirth. In 1940, Landsteiner and Wiener discovered a new antigen in erythrocytes, which they called Rh. Subsequently, it was demonstrated that immune body reactions were responsible for certain hemolytic reactions in transfusions and for the occurrence of erythroblastosis fetalis. The Rh groups were studied intensively by American and British workers, under the stimulus of the wartime expansion of blood transfusion services. The genetic relationships of the various Rh groups were anticipated, and, in fact, several genotypes were predicted prior to their actual discovery.

In 1943 the British geneticist, R. A. Fischer, made a theoretic analysis of the problem and concluded that the presence of three closely linked genes in one pair of chromosomes could explain the observations. These he designated C, D and E. It is possible to specify the genetic and antigenic constitution of any person in these terms, e.g., cde/cde (Rh negative) and cDe/cDe (Rh positive). In the United States, the genetic constitution is usually indicated by the "short symbol" of Wiener and his associates, e.g., rr and Ro Ro. In spite of the complexity of these two systems, it is obvious that the well trained internist must have at least a working knowledge of this revolutionary subject.

This Medical Research Council memorandum is the most authoritative and easily understandable summary of present knowledge available on this subject. The first section, by Race, is an admirable and concise presentation of the Rh groups, the different Rh antibodies and the genetic basis of the Rh groups. The second section, by Mollison, is devoted to clinical consideration as related to blood transfusions and the management of erythroblastosis fetalis.

The final section, by Mourant, describes in detail approved methods for Rh testing, the circumstances in which the tests should be applied and the proper interpretation of them.

At the present time, it is accepted that the transfusion of incompatible blood is a grave mistake, except in dire emergencies. This 74 page memorandum provides all the information necessary to appreciate the importance of the Rh groups and to manage properly the Rh negative patient. It is highly recommended for all concerned with blood transfusions and with pregnant women.

Cardiovascular Disease in General Practice By Terence East, M.A., D.M. (Oxon.), F.R.C.P. (London). Third edition. Price, 15s. Pp. 218, with 34 illustrations. London: H. K. Lewis & Company, Ltd., 1949.

This small booklet is planned for the general practitioner, and it contains most practical material. Its aim is to give clear, succinct and practical information "seasoned with sane comment." The commonest heart diseases and disorders are described briefly in the twenty-one chapters, some of them being just mentioned

in a few words. New advances of medicine are also included. Electrocardiography has been omitted with purpose, because "a little learning is a dangerous thing."

The author describes, in clear and simple style, the nature of each disorder, its clinical picture and diagnosis, prognosis and treatment. General treatment is condensed in a special chapter. There are several drawings, illustrating different shapes of the heart, etc.

This book can be recommended as a time saver.

More Than Armies. The Story of Edward H. Cary, M.D. By Booth Mooney, M.D. Price, \$5. Pp 270. Dallas, Texas: Mathis, Van Nort & Co., 1948.

This is an excellent medical biography. Here is unfolded the story of one of medicine's elder statesmen, Dr. Edward Henry Cary, a distinguished ophthalmologist, a former president and trustee of the American Medical Association, founder and president of the Southwestern Medical Foundation, Chairman of the Board of the National Physician's Committee for the Extension of Medical Care and a member and high office holder in many medical societies and civic organizations.

Dr. Cary continually preached as well as practiced the adoption of the highest standards of education, of conduct and of medical service. He has steadfastly defended the American system of medical practice against any threat of federal or state bureaucracy or "political" control because of his conviction that such a change would not be in the best interest of either the people or the medical profession.

On Feb. 28, 1947, the occasion of his seventy-fifth birthday, the officers and trustees of the Southwestern Medical Foundation honored Dr. Cary with a dinner at which there were over five hundred citizens of Dallas and its environs and many leaders in medicine from the various states. Dr. Cary was lauded not alone for his natural endowments but also for the direction of his leadership. Dr. Morris Fishbein, editor of *The Journal of the American Medical Association*, gave the principal address and in summation said: "This man is a physician, a distinguished scientist, a medical statesman, a great builder, an educator, an idealist—all combined in the person of one dynamic, driving, courageous and at the same time gentle, friendly and affectionate human being."

The author brings this biography to a close with the following statement: "Dr. Cary has built his own enduring monument and lived to see that it is good. A man could hardly ask for more."

An Introduction to Cardiology By Geoffrey Bourne, M.D., F.R.C.P. Price, \$4.50. Pp 264, with 64 illustrations. Baltimore: Williams & Wilkins Company, 1949.

This little book does not seem to add much to what is already available in textbook form. On the whole, the concise statements are adequate, and the numerous reproductions of electrocardiograms and roentgenograms are helpful. It is of interest that the classic prescription for the treatment of auricular flutter, long since thought obsolete by many, is preserved. The book is extremely well written, the example of the old lady running around the lamppost (page 99) gives a good idea of what quinidine does in auricular fibrillation, although even the established concept of circus movement has recently been questioned.

The Digestive Tract in Roentgenology By Jacob Buckstein, M D Price, \$16
Pp 889, with 1,030 illustrations Philadelphia J B Lippincott Company, 1948

This volume is a summary of the information obtained by the author during twenty-five years of experience in correlating the roentgenographic findings with those obtained at operation and autopsy from an enormous amount of material The author's previous book "Clinical Roentgenology of the Alimentary Tract" is well known and has served as a valuable textbook

There are sixty-five chapters divided into the following nine sections Introduction, the Hypopharynx and Esophagus, the Stomach, the Duodenum, the Small Intestine, the Large Intestine, Herniation and Eventration of the Diaphragm, the Gallbladder and Bile Ducts and the Spleen, Liver and Pancreas The book is fairly comprehensive, and considerable space is devoted to the more common gastrointestinal lesions

The technical procedures necessary for accurate examination are covered in detail In each section the roentgen findings of the normal organ are discussed The important clinical findings are integrated with the roentgen signs, and many illustrative case histories are included

There are numerous excellent illustrations, and the text is clear, detailed and well written This volume is a necessary addition to the library of every physician and surgeon interested in the gastrointestinal tract

Clinical Aspects and Treatment of Surgical Infections By Frank Lamont Meleney, M D Price, \$12 Pp 840, with 287 illustrations Philadelphia W B Saunders Company, 1949

Dr Meleney has written thoroughly on the subject of surgical infections He speaks with authority, since he has been a surgeon for twenty-five years and, during this time, has been a pioneer in establishing the importance of integrating the bacteriologic laboratory with the surgical service

The book contains a review of the so-called surgical infections as they affect various organs and tissues of the body In addition to covering Dr Meleney's own experience, the book contains chapters written by some of his colleagues at the Presbyterian Hospital, including Drs Lockwood, Harvey, Longacre and Sandusky

Correlated with the studies on surgical infections are descriptions of contributing etiologic factors and surgical therapy The place of antibiotic therapy and the sulfonamide drugs in the treatment of infections has been considered in every phase of the subject The last chapter deals with surgical infections in war wounds, and it is very interesting

The book is an excellent addition to the library of any physician or surgeon and is equally valuable for medical students

Mycoses and Practical Mycology By N Gohar Price, \$6 Pp 234, with 134 illustrations Baltimore The Williams & Wilkins Company, 1949

This book simplifies, for the student and the clinician, a difficult and neglected problem It should prove extremely useful because it is brief, somewhat dogmatic and profusely illustrated Therapy is simplified, and only the accepted methods are discussed The volume is highly recommended

The Uses of Penicillin and Streptomycin By Chester S Keefer, M D
Price, \$2 Pp 72 Lawrence, Kan The University of Kansas Press, 1949

The Porter Lectures for 1949, given under the auspices of the University of Kansas School of Medicine, appear under the imprint of the University of Kansas Press in a neat and attractive volume The three lectures given by Dr Chester S Keefer deal with the uses of penicillin and streptomycin, as well as other antibacterial agents from microbes No one is better fitted to discuss this subject than Dr Keefer, and his precise and lucid summary of the subject makes interesting as well as useful reading

Coronary Heart Disease By A Carlton Ernstene, M D Price, \$2 50 Pp 95
Springfield, Ill Charles C Thomas, 1948

In this monograph the author presents in a readable form the elementary concepts of the subject of coronary heart disease The various manifestations of the condition are considered from the standpoint of lesions present, clinical findings and treatment The criteria presented for diagnosis and the methods of treatment outlined are widely accepted The monograph has little to offer the advanced student or the practitioner who has any considerable contact with patients suffering from coronary heart disease In the discussion on the electrocardiographic changes seen in coronary disease, the absence of figures illustrating such changes makes their visualization by the reader much more difficult

Cardiac Catheterization in Congenital Heart Disease By A Cournand,
M D, Janet S Baldwin, M D, and A Himmelstein, M D Price, \$4 00
Pp 108 New York Commonwealth Fund, 1949

This brief monograph is based on an exhibit on the subject previously presented by the authors The material is clearly and concisely presented in relatively few pages It is supplemented by many diagrams and illustrations Theoretic data are presented in the initial pages, and the results of studies of actual cases in the remainder The cyanotic group of congenital defects was intentionally omitted This fine work is to be highly recommended to all persons interested in the problem It is particularly useful to beginners, since it is written in a clear and simple fashion and includes detailed specifications of materials, technic and source of equipment for catheterization of the heart

The Literature on Streptomycin 1944-1948 By Selman A Waksman Price,
\$3 Pp 112 New Brunswick, N J Rutgers University Press, 1948

This volume, which consists of 1,171 references on streptomycin for the years 1944 to 1948, 12 references dealing with actinomyces and 16 with streptothricin, and which is indexed by author and subject, is not suitable for review

Posttraumatic Epilepsy By A Earl Walker, M D Price, \$2 75 Pp 90,
with 28 illustrations Springfield, Ill Charles C Thomas, Publisher, 1949

Although this little book contains an admirable discussion of all the features of the post-traumatic epilepsies, it is not unnatural that the author should be especially concerned with the surgical treatment of these disorders His experience includes over 200 cases, and the results, both of medical therapy and of operation, are analyzed The book is finely printed and illustrated, there are an index and a bibliography

Symposium on Treatment of Long-Term Illness The Medical Clinics of North America Pp 314, with 165 illustrations Philadelphia W. B. Saunders Company, 1949

This volume follows the general familiar pattern of the others in the series "Long term illness" means little from the standpoint of classifications, so one finds a great variety of conditions dealt with—for example, cardiac, pulmonary and hepatic disease. Most of the writers are authorities in their field, and have written good summary articles, the volume definitely makes interesting and useful reading.

A M A Interns' Manual Price, \$2.25 Pp 201 Philadelphia W. B. Saunders Company, 1948

This is a useful little book which should prove to be of value to the intern. Laboratory and clinical data, drugs and their dosage, materia medica, acute poisoning, diet and nutrition and physical medicine are among the subjects discussed. These problems are presented concisely and briefly in a small, easily portable handbook of 201 pages.

TUSSIVE SYNCOPE

Observations on the Disease Formerly Called Laryngeal Epilepsy,
with Report of Two Cases

WILLIAM S McCANN, M D

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FRANK W LOVEJOY Jr, M D

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AND

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IN 1876, Charcot¹ described the syndrome of laryngeal vertigo,² characterized by the loss of consciousness after severe coughing. Since then, occasional cases have been described, and in some instances the unusual vigor of coughing, associated with a respiratory infection, such as pertussis, may have been important. Whitty³ reviewed nearly 100 of these cases in 1943, adding 4 more, and stated that he felt that epilepsy was an important factor despite rather meager evidence. He quoted De Havilland Hall, who in 1894 called attention to the large number of middle-aged plethoric males with laryngitis or bronchitis in a series of these cases. Wilkins and Friedland⁴ observed that some normal subjects could lose consciousness by performing the Valsalva

From the Chest Laboratory, Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical, Surgical and Psychiatric Clinics, Strong Memorial Hospital and Rochester Municipal Hospital.

1 Charcot, J M. Statement to the Societe de Biologie, Nov 19, 1876, *Gaz med de Paris* 5 588, 1876, Description of "la grande attaque hysterique," *Progr med* 7 17, 1879.

2 In 1679, Thomas Sydenham (cited by Major, R H. *Classic Descriptions of Disease*, ed 3, Springfield, Ill, Charles C Thomas, Publisher, 1945, p 201) described the severe cough of patients seen in an epidemic of respiratory disease resembling influenza and noted that "the cough occasioned such violent motion of the lungs, that sometimes a vomiting and vertigo ensued."

3 Whitty, C W M. On the So-Called "Laryngeal Epilepsy," *Brain* 66 43, 1943.

4 Wilkins, R W, and Friedland, C K. Laryngeal Epilepsy Due to Increased Intrathoracic Pressure, *J Clin Investigation* 23 939, 1944.

experiment of forced expiration against a closed glottis, in addition, diminished venous return and cardiac output were recorded by the ballistocardiographic method. The authors described 2 patients with pulmonary disease with similar signs, in 1 of them voluntary coughing could produce loss of consciousness. In 1946, Rook⁵ observed 3 examples of syncope due to coughing in 500 cases of loss of consciousness in personnel of the Royal Air Force and questioned the importance of epilepsy, favoring the concept of cerebral congestion and anoxia instead.

Three more cases of this syndrome have been recorded recently, the first 2 are described in detail in this paper. The third patient could not be studied by cardiac catheterization because of pulmonary embolism from thrombophlebitis in the legs. However, the association of syncopal attacks with coughing made possible the presumptive diagnosis of tussive syncope.

REPORT OF CASES

CASE 1—A male schoolteacher of 42 had had repeated episodes of fainting associated with coughing for the past three years. On some occasions he had fallen, once fracturing some ribs, whereas with less severe coughing he usually became lightheaded and confused and felt tingling of the hands and feet. He had occasionally been observed to have a brief clonic convulsion, complete loss of consciousness did not occur while he was recumbent, however. He had smoked two to three packs of cigarets daily for years and ingested large quantities of coffee.

Physical Examination—The patient was a short man with a moderately obese abdomen. There was some tachypnea with a rate of 20 to 30 respirations per minute, but no evidence of orthostatic hypotension as the recumbent blood pressure of 115 systolic and 88 diastolic rose to 122 systolic and 90 diastolic on standing. The voice was husky, and the nasopharynx was chronically congested. Chest expansion was slightly limited, and the bronchovascular markings in the roentgenogram of the chest were more prominent than usual. The results of studies of the blood, glucose tolerance tests and lumbar puncture were all normal, as were the electroencephalogram and electrocardiogram. Neither massage of the carotid sinus, hyperventilation nor venous congestion of the head produced by a pressure cuff around the neck at 50 mm of mercury caused syncope. Performance of the Valsalva maneuver of forced expiration against a closed glottis caused congestion of the face and head, disappearance of heart sounds and inability to obtain the blood pressure, followed within fifteen seconds by a grand mal convulsion.

Laboratory Examination—Studies done in the chest laboratory demonstrated a mild degree of pulmonary insufficiency. Fluoroscopic examination of the chest showed decreased diaphragmatic excursion, and the total volume of the lungs was found to be reduced to 85 per cent of the predicted value, whereas the volume of residual air was 30 per cent of the total capacity (table 1). Slight hypoxemia was shown by the reduction of the arterial oxygen tension to 79 mm and the oxygen saturation to 93.6 per cent. During an exercise tolerance test⁶ there was considerable hyperventilation and diminished respiratory efficiency.

5 Rook, A. F. Coughing and Unconsciousness. The So-Called Laryngeal Epilepsy, *Brain*, **69** 138, 1946.

6 Bruce, and others. Normal Respiratory and Circulatory Pathways of Adaptation in Exercise, *J. Clin. Investigation*, to be published.

(fig 1) The ballistocardiogram was abnormal in pattern and irregular in amplitude except after the patient was exposed to cold or after the Muller experiment. Under these circumstances there was marked bradycardia with a rate of 52 to 60 beats per minute.

A cinefluorogram, obtained at the rate of 60 frames per second for five seconds during a paroxysm of coughing, showed appreciable bulging of the right atrium, the venae cavae and the pulmonary conus and greater density of the hilar root shadows, attributed to the momentary "trapping" of blood within the pulmonary circulation (fig 2).⁷

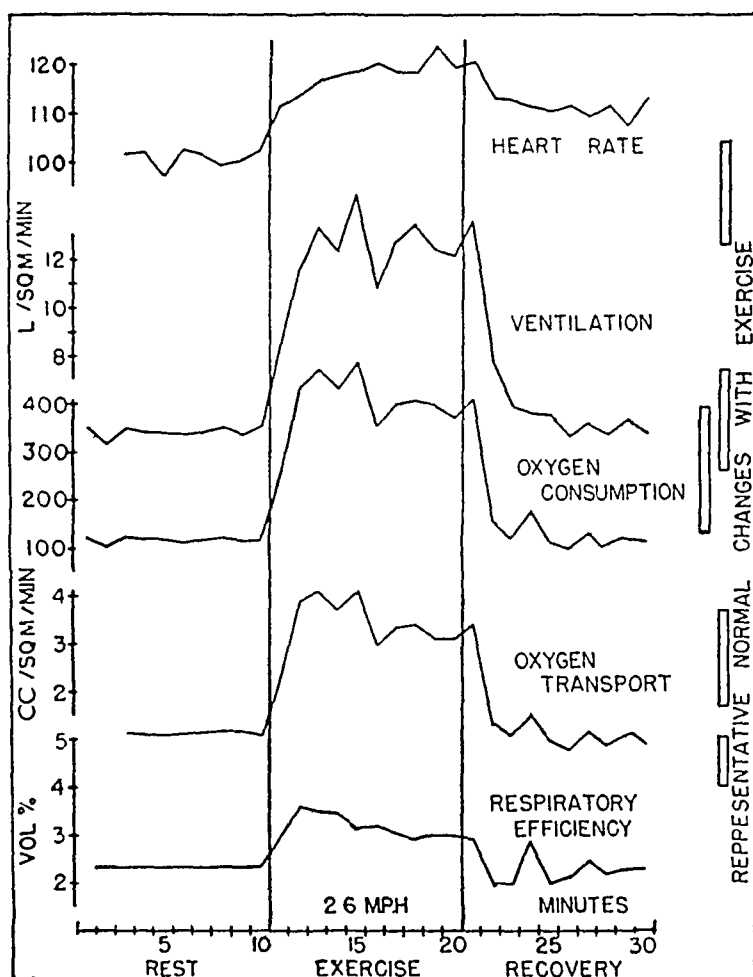


Fig 1—Exercise tolerance in case 1. Note the tachycardia, hyperventilation and decreased respiratory efficiency (volumes per cent of oxygen absorbed from room air) throughout the test.

On another occasion, with an indwelling needle in the femoral artery, a prompt transient rise in pressure occurred in the Valsalva maneuver, followed by a marked drop in pressure which persisted for several seconds until climaxed by a convulsion (fig 3 C). The electrocardiogram revealed no asystole during this interval.

Cardiac catheterization not only showed the usual decrease in net pulse pressure in the right ventricle in the Valsalva maneuver (fig 3 B), with a reduction in systemic pulse pressure, but also revealed the extraordinary pressures that could develop inside the right ventricle during a paroxysm of coughing (fig 3 A).

7 The cinefluorogram was made in the department of radiology.

TABLE 1—Laboratory Data in Case 1

	Value Predicted from Height	Value Observed	$\frac{\text{Value Observed}}{\text{Value Predicted}} \times 100, \%$
Lung Volumes			
Vital capacity	3 80 L	2 90 L	76
Residual air	1 13 L	1 27 L	112
Total capacity	4 93 L	4 17 L	85
Residual air	23%	30%	
Venous Pressure			
Patient recumbent, resting	9 6 cm (no increase with pressure over right upper quadrant of abdomen)		
Patient recumbent, following ambulatory activity	16 7 cm (increased to 18 7 cm with vigorous coughing)		
Circulation Times			
Arm to tongue, with ether	18 sec		
Arm to mouth, with maceasol 1 ⁰	18 5 sec		
Catheterization Studies			
Arterial blood	1	2	3
Tension, mm			
CO ₂	42		38
O ₂	79		73
Content, vol %			
CO ₂	42 4		43 7
O ₂	18 0		16 5
Venous blood			
Tension, mm			
CO ₂	40	49	45
O ₂	38	32	35
Content, vol %			
CO ₂	47 2	47 5	46 9
O ₂	17 4	10 4	12 5
Arterioventricular difference, vol %	4 6		4 4
O ₂ consumption, cc /min	218	186	197
Cardiac output, L /min	4 75		4 34
O ₂ capacity, vol %	19 20		18 44
O ₂ saturation of arterial blood, %	93 8		89 5
Maximum systolic pressure in right ventricle, patient resting, mm	28	41	17

Many pressures over 200 mm were observed,⁸ as in other patients (fig 4), the maximal pressure recorded in this patient was 300 mm. Significantly high pressures

8 That the coughing pressures observed were not artefacts in recording may be seen from the calibrations (fig 3), revealing no overshooting of a fixed pressure, and from the records of coughing obtained during cardiac catheterization of other patients (fig 4). None of these patients experienced tussive syncope at any time, and the maximal pressures in the right ventricle or the pulmonary artery during coughing ranged from 50 to 150. The values reported by W F Hamilton, R A Woodbury and H T Harper Jr (Arterial, Cerebrospinal and Venous Pressures in Man During Cough and Strain, *Am J Physiol* **141** 42, 1944) and by H D Laussen, R A Bloomfield and A Courmand (The Influence of Respiration on the Circulation of Man, *Am J Med* **1** 315, 1946) were up to approximately 140 mm. We recorded a pressure of 125 mm for 1 patient with advanced cystic disease of the lungs (but no symptoms), the highest pressure in these control studies was 150 mm, in a patient with chronic granulomatosis of the lungs associated with exposure to beryllium compounds. A further check of the pressure recording for the patient with tussive syncope was the diastolic pressure of 70 mm in the right ventricle, which was observed while he blew against a column of mercury with an air pressure of 70 mm.

were sustained long enough to demonstrate a pronounced reduction in the systemic arterial pressure to 60 systolic and 50 diastolic. After the paroxysm of coughing, the net pulse pressure in the right ventricle recovered more rapidly than the systemic

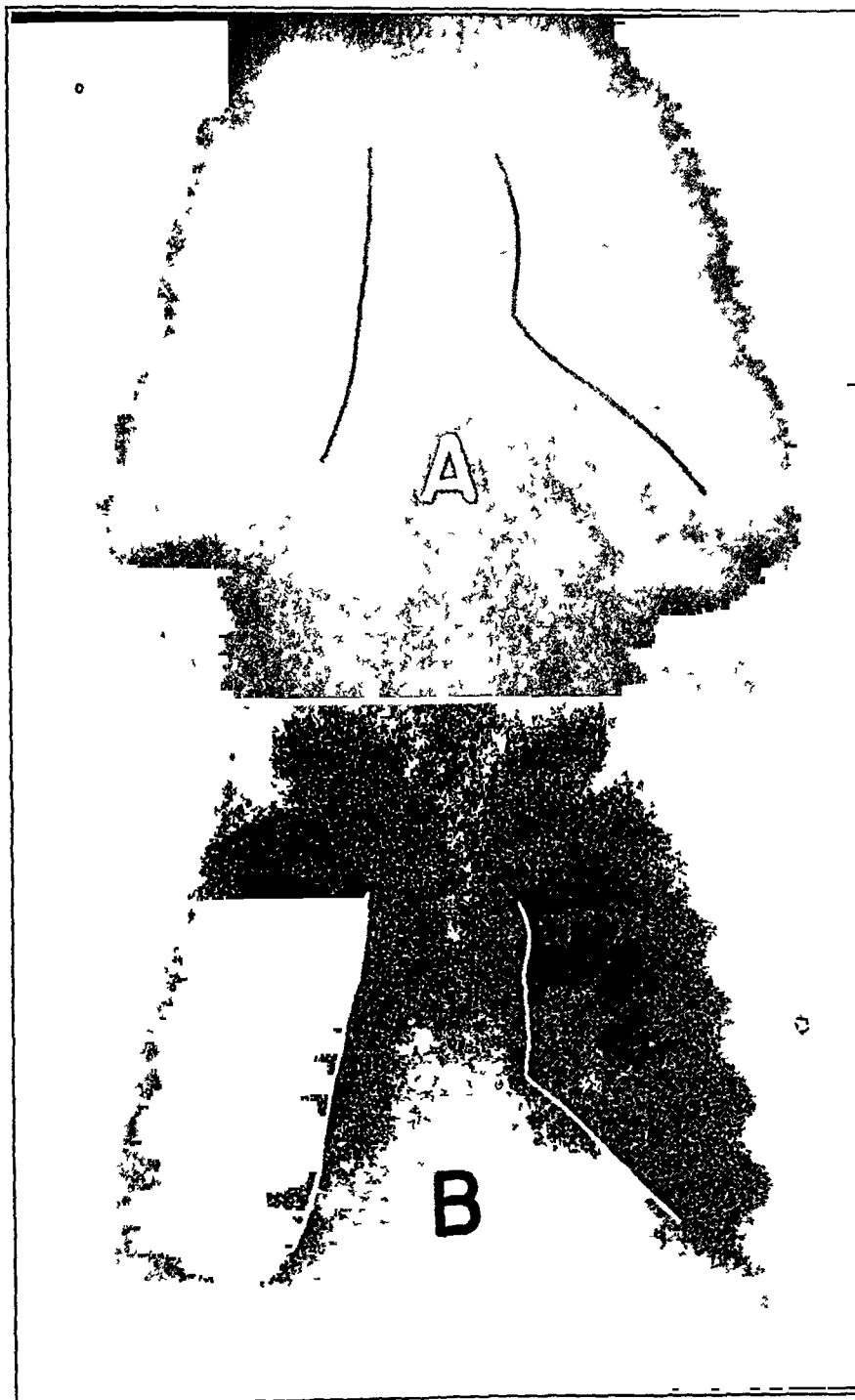


Fig 2—Selected enlargements from a cinefluorogram of the chest in case 1. *A*, expansion of the superior mediastinum, the right atrium, the pulmonary conus and the hilar shadows during quiet breathing, *B*, during coughing.

pulse pressure. Even with mild coughing the patient usually experienced transient lightheadedness and confusion, concomitantly the arterial oxygen tension was reduced by 20 mm and the oxygen saturation by 6 per cent.

In order to ascertain whether the registered pressures in the right ventricle during coughing were entirely due to increased intrathoracic air pressure or were in part due to spasm of the pulmonary artery, the following observations were made. Cardiac catheterization was repeated, and a bronchoscope was placed in the trachea.⁹ No laryngeal or bronchial obstruction was seen. Under these circumstances the patient was entirely unable to perform the Valsalva maneuver. He was

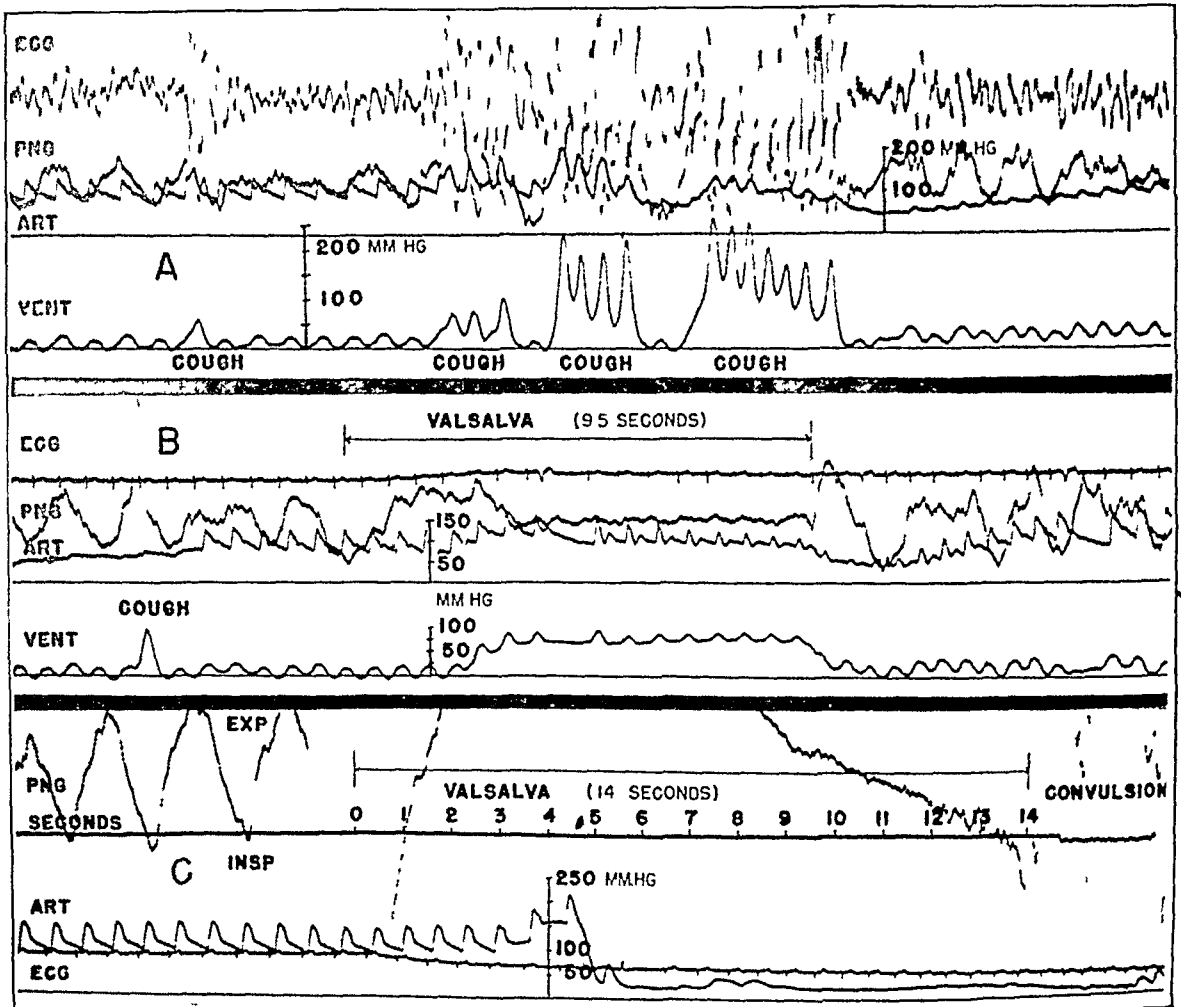


Fig 3—Hemodynamic records in case 1. *A*, the ballistocardiogram (BCG), the pneumogram of the chest (PNG), the intra-arterial pressure from the radial artery (ART) and the pressure in the right ventricle (VENT) during several paroxysms of coughing. During the last paroxysm pressures of 250 mm were recorded, following the coughing, the arterial pressure dropped to 50 mm and returned only slowly, during those few seconds the patient felt dizzy and confused. *B*, changes during a Valsalva experiment of short duration. The pulse pressure in both the radial artery and the right ventricle decreased toward the end of the effort. *C*, record of pressures in the femoral artery during a Valsalva experiment of longer duration. The return of the tracing in the pneumogram to the base line during the prolonged forced expiration was an artefact. Following a transient rise there was a sharp drop in arterial pressure to 50 mm in the interval of 1 heart beat. Thereafter, there were no effective pulse beats until shortly after a convulsion had occurred, despite a normal sinus rhythm as shown in the electrocardiogram.

⁹ The bronchoscopic examination was made by Dr E B Emerson Jr.

able to cough with considerable expulsive force, and the pressure in the right ventricle rose as high as 250 mm (table 2). The endotracheal air pressure after removal of the bronchoscope was as high as 200 mm with coughing. It should be noted, too, that although the patient was able to maintain the Valsalva experiment for as long as thirty-four seconds he did not lose consciousness.

Later Studies—Two months later, the patient returned for further studies and stated that he had been coughing less and had had no further syncopal attacks. Whereas he had formerly shown borderline hypertension in the pulmonary circulation, especially with leg exercises, he then exhibited normal pressures in the

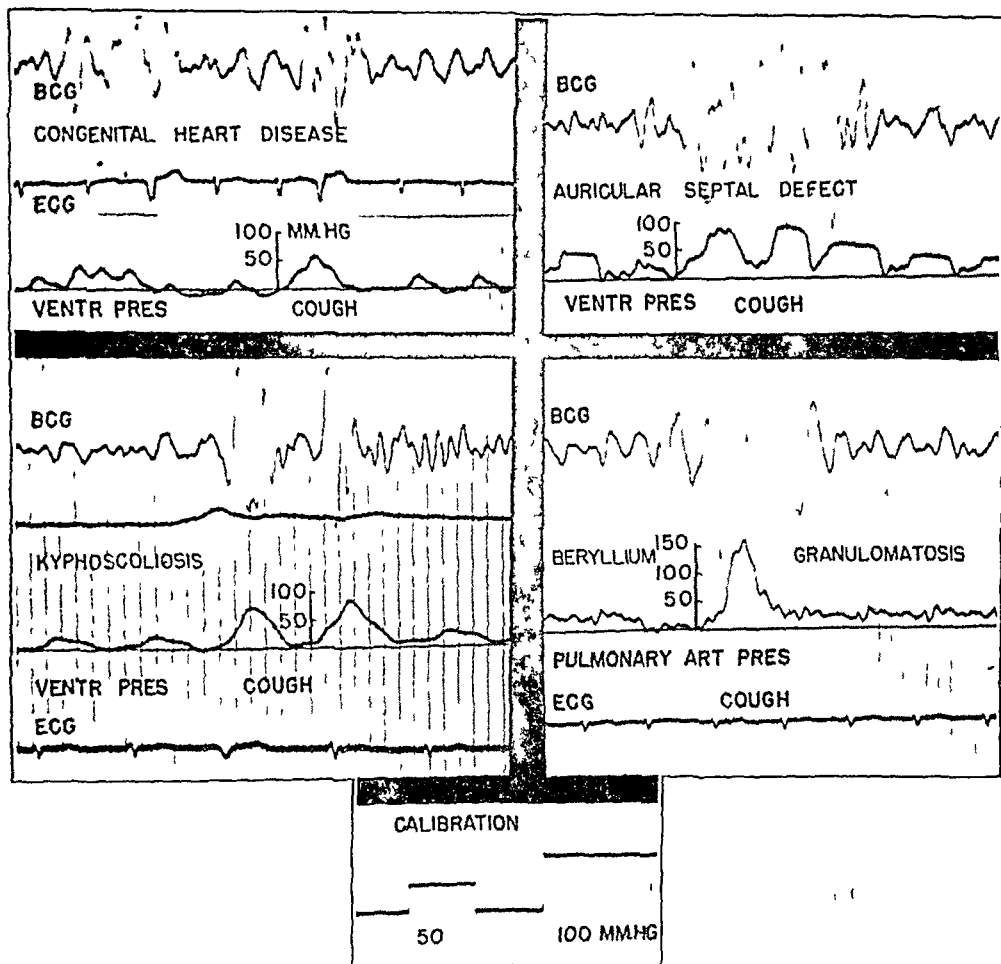


Fig 4—Intracardiac pressures during coughing in 4 patients studied for other conditions. Note the lack of overshooting in the calibration records.

right ventricle and the pulmonary artery, as determined by a third cardiac catheterization (table 2). The diastolic pressure in the right ventricle rose to 78 mm on performance of the Valsalva maneuver (held for thirty-seven seconds) and to 255 mm with coughing, but in neither instance was there any loss of consciousness. The vasodilating effects of amyl nitrite, tetraethylammonium chloride (3.5 cc intravenously, 5 mg per kilogram of body weight) and aminophylline were investigated. The first two medicaments caused the sensation of peripheral tingling, but no other effects. After only 0.09 Gm of aminophylline U.S.P. had been given intravenously over two to three minutes' time, the patient experienced pain in the

left side of the chest, which was aggravated by deep breathing. This persisted for about half an hour and was unassociated with any changes in the heart rate, the blood pressure or the oxygen consumption or in the electrocardiogram or ballistocardiogram. Following oxygen therapy by mask the pain promptly disappeared. The pressure in the right ventricle during coughing was only 116 mm, but it seemed that the lower pressure on this occasion was due to the lessened vigor of coughing because of the pain in the chest rather than to a specific vasodilating effect of aminophylline on the pulmonary arterial tree. It could, of course, have been an expression of both factors. After these observations were made, oxygen was administered by mask and the pain promptly disappeared.

The patient experienced repeated episodes of syncope associated with coughing. He presented the features of abdominal obesity and mild pulmonary insufficiency. The Valsalva maneuver abruptly altered the hemodynamics of the pulmonary circulation by virtue of the increased

TABLE 2—Pressures* in Case J

Maximal pressures during second catheterization		Coughing	Valsalva Experiment	Duration of Valsalva Experiment, Seconds
Location	Resting			
Trachea		200	109	
Right ventricle	41	260	75	26
Right ventricle (bronchoscope in trachea)	22	260	22	
Effects of drugs on pressure in right ventricle				
Drug				
None	17	255	78	27
Amyl nitrite U S P	22			
Tetraethylammonium chloride	17	172	55	
Aminophylline U S P	17	116	50	

* Mm of mercury

intrathoracic pressure (as postulated by Wilkins and Friedland⁴), which resulted in impaired cardiac output and in cerebral anoxia. On some occasions this procedure precipitated a convulsive seizure. Extraordinarily high pressures in the right ventricle, together with fluoroscopic evidence of the trapping of blood within the pulmonary circulation, were also observed during paroxysms of coughing. The mechanism of these changes in pressure was believed to be identical with that of the Valsalva maneuver. The pressure in the right ventricle during coughing and during the Valsalva maneuver was lower following the intravenous administration of either tetraethylammonium chloride or aminophylline. The untoward response of substernal pain to the latter drug made the interpretation difficult. There were no objective changes in the cardiac mechanisms during this painful episode, but the administration of oxygen relieved the symptomatic distress. Bronchoscopic intubation of the trachea failed to prevent the high pressures which occurred in the right

ventricle with coughing. Hence, this patient could produce not only high intrathoracic air pressures but also equally high, or higher, vascular pressures proximal to the pulmonary artery. Consequently, the possibility of spasm of the pulmonary artery could not be overlooked.

CASE 2—J S, a 49 year old metal sorter, had had a chronic cough for the past few years. During the previous fourteen months, he had experienced several

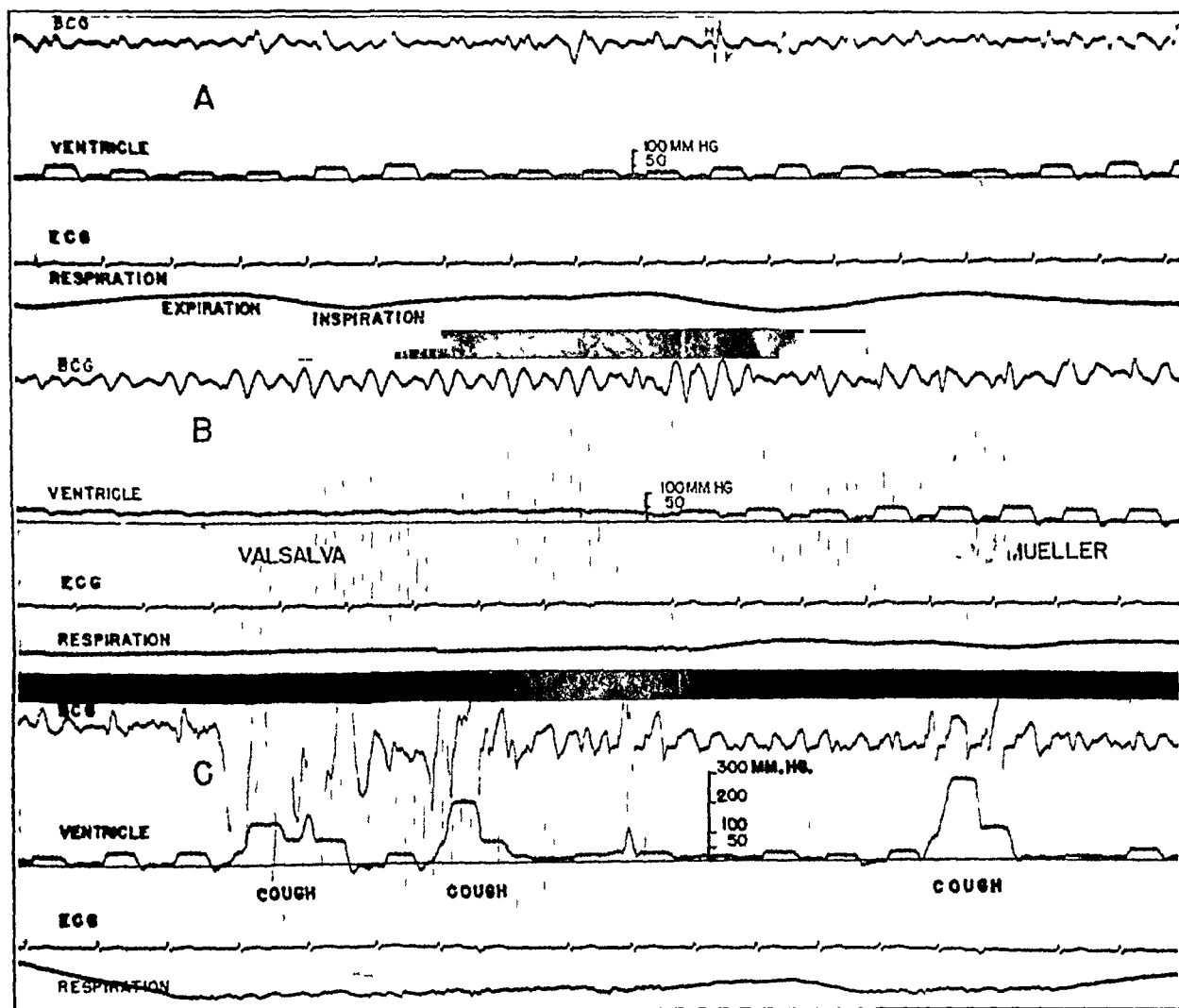


Fig 5—Intracardiac pressures in case 2. *A*, marked respiratory variations in pressure in the right ventricle. Note that the ballistocardiogram (BCG) also varied with respiration and that the configuration became normal only in inspiration. *B*, partial record of the end of a Valsalva experiment and the beginning of a Muller test. The pulse pressure in the right ventricle almost disappeared during the Valsalva experiment. *C*, the high pressures in the right ventricle during coughing (up to 270 mm).

syncopal attacks occurring after severe bouts of coughing, usually following meals. Despite the fact that each time he had fallen backward, he had suffered no serious injury. His only other complaint was slight exertional dyspnea. He smoked about one and a half packs of cigarets daily.

Physical Examination—The patient was a short, plethoric man with abdominal obesity. The anteroposterior diameter of the chest was somewhat increased, with slightly less expansion of the chest on the left side. Auscultation of the heart and lungs was noncontributory.

Laboratory Examination—Fluoroscopic examination of the chest was unremarkable except for slight prominence of the pulmonary conus. Determination of the lung volumes revealed a moderate amount of emphysema with an increase of the residual air to 46 per cent of the total capacity. The venous pressure was elevated to 15 cm of water and increased 0.5 cm with pressure over the liver.

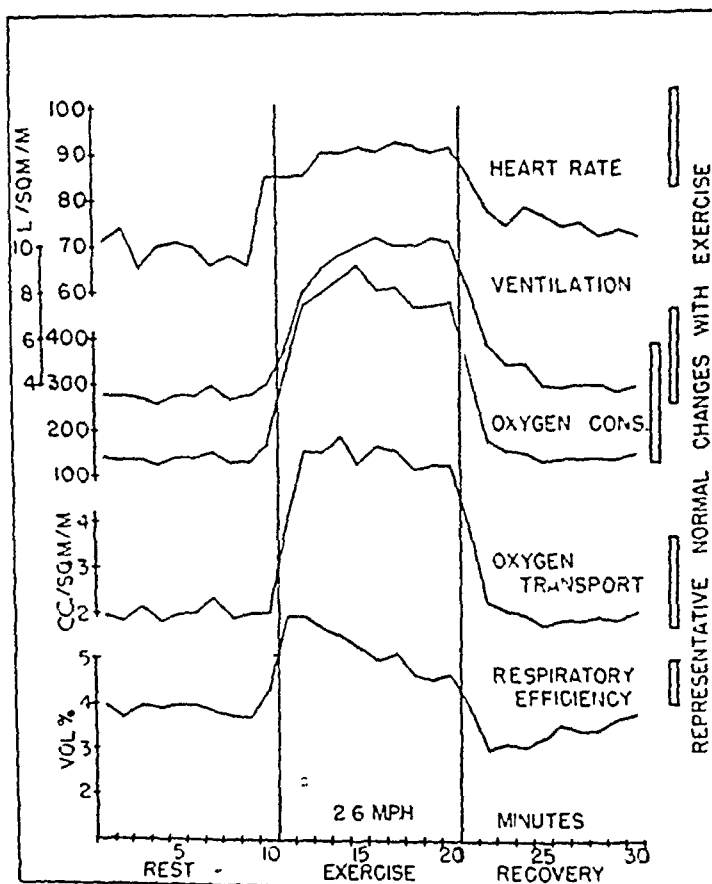


Fig. 6—Exercise tolerance test in case 2, showing a comparatively normal performance.

Circulation times (determined with ether and macasol¹⁰) were within normal limits. The electrocardiogram was normal, but the ballistocardiogram showed an abnormal pattern (fig 5A). An exercise tolerance test on a motor-driven treadmill at 2.6 miles per hour for ten minutes showed no gross abnormality, but the patient experienced moderate dyspnea (fig 6).

Cardiac catheterization was performed, pressures up to 270 mm in the right ventricle were recorded with mild coughing (fig 5C). There was no symptomatic

¹⁰ Each 2 cc ampul of macasol contains the following: magnesium sulfate, 0.680 Gm; magnesium gluconate, 0.324 Gm; calcium sulfate, 3.2 mg; and copper sulfate (as preservative), 0.02 mg.

distress, but the patient was reluctant to cough hard or long because of painful symptoms from a previously repaired inguinal hernia on the right side. During quiet breathing the pressure in the right ventricle in systole varied from 18 systolic and 0 diastolic to 41 systolic and 5 diastolic at the peak of expiration and inspiration, respectively (fig 5A). The pulse pattern and the net pressure in the right ventricle during the Valsalva maneuver were greatly reduced (fig 5B). The arterial blood was 93.6 per cent saturated, with an oxygen tension of 59 mm.

Despite the failure to demonstrate syncope following cough, the body build, the exaggerated respiratory variation of pressures in the right ventricle, the increased residual air and the acute elevation of pressure in the right ventricle to 270 mm with coughing were all features compatible with this syndrome. It was felt that observations during an acute paroxysm of coughing might confirm the diagnosis, as in the first case.

COMMENT

Abnormally high pressures in the right ventricle during coughing were obtained in both patients studied. In the first case it was fairly well established that the syncope and convulsions resulting from paroxysms of coughing or from the Valsalva maneuver were caused by congestion of the cerebral veins, decreased cardiac output and anoxemia. The second patient, though not exhibiting syncope or convulsions while under observation, presented clinical and laboratory evidence similar to the first patient, and it is assumed that syncope would have occurred had he been able to sustain either the cough or the Valsalva maneuver. Studies of the first patient to elucidate the mechanism of the pressures in the right ventricle with coughing were inconclusive. The possibility of a reflex spasm of the pulmonary artery existed in view of the fact that the same high pressures in the right ventricle with coughing were produced with a bronchoscope in the trachea.

The importance of nicotine inhaled from smoking tobacco in these reactions deserves a comment. The initial application of nicotine to the sympathetic ganglions supplying the lungs of experimental animals (dogs) causes vasoconstriction, and the late effect is that of paralysis of the ganglions.¹¹ Whether or not the excessive smoking of cigarettes could permit the absorption of nicotine in sufficient quantity to cause pulmonary vasoconstriction cannot be answered at the time of writing.

From these considerations it seems that the term "tussive syncope" is more appropriate for this syndrome than "laryngeal epilepsy," since the syncopal response is dependent on circulatory disturbances due to coughing and is not due to epilepsy.

11 Daly, I. de B., Duke, H., Heff, C. O., and Weatherall, J. Pulmonary Vasomotor Fibers in the Sympathetic Chain and Its Associated Ganglia in the Dog, *Quart J Exper Physiol* **34**: 285, 1948.

SUMMARY

The background of Charcot's syndrome of laryngeal epilepsy is briefly reviewed, and the laboratory findings in 2 similar cases are described. Both the Valsalva maneuver and paroxysmal coughing were found to impede venous return and pulmonary circulation and to decrease cardiac output, confirming the findings of Wilkins and Friedland.⁴ Cerebral congestion alone was not sufficient to cause syncope, but cerebral congestion occurred in addition to anoxemia and cerebral anoxia. In the first patient, syncope and even convulsions were produced by the Valsalva maneuver while he was in the recumbent position. The possibility that spasm of the pulmonary artery occurred, in addition to a pronounced increase in intrathoracic air pressure, was investigated with inconclusive results. The term "tussive syncope" is believed to be more appropriate than "laryngeal epilepsy."

AUREOMYCIN TREATMENT OF PNEUMOCOCCIC PNEUMONIA

Clinical and Laboratory Studies on Thirty-Three Patients

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BOSTON

AUREOMYCIN is an antibiotic which, from the results of early studies in vitro and in experimental infections, as well as in initial clinical trials, appears to have a wider range of activity than its successful antecedents, penicillin and streptomycin¹. This range encompasses most of the known causative agents of the acute pneumonias, including the gram-positive and gram-negative bacteria, the organisms of the psittacosis-lymphogranuloma venereum group and the Q fever and other rickettsias. Since aureomycin was also found to be effective when given by mouth and was essentially free of serious toxic effects, it seemed particularly suitable for extended clinical trials in cases of pneumonias of diverse origin.

During the past year an attempt was therefore made to evaluate the therapeutic effectiveness of aureomycin in the various types of pneumonia and in some of the other severe acute infections of the respiratory tract that were available for study. The present paper deals with the results of the clinical and laboratory studies made on 33 consecutive

Aided by a grant from the United States Public Health Service

The aureomycin was provided by the Lederle Laboratories, Division of American Cyanamid Company, Pearl River, N. Y.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

1 Duggar, B. M., and others. Aureomycin: A New Antibiotic, *Ann. New York Acad. Sc.* **51**: 175-342 (Nov. 30) 1948.

patients with pneumococcic pneumonia who were treated with this agent. The findings in various other groups of cases are presented in separate communications ²

MATERIALS AND METHODS

Selection of Cases—The 33 patients included in this study were all admitted to the adult medical wards of the Boston City Hospital before June 15, 1949. Before any aureomycin was given these patients satisfied all the following criteria: 1. In each case the history and findings by physical examination were consistent with a diagnosis of pneumococcic pneumonia. Roentgenograms of the lungs were usually taken at the time of admission to the hospital, but occasionally they were taken a day or two later, these also showed lesions consistent with pneumococcic pneumonia in each instance. 2. All patients were acutely ill and febrile at the time the first dose of aureomycin was given. 3. No previous treatment with anti-serums, sulfonamides or antibiotics had been given. 4. Blood and sputum were obtained for cultures, and pneumococci of specific types were isolated and identified from one or both of these sources. All patients with pneumococcic pneumonia who satisfied these criteria have been included, and, in fact, no patient with pneumococcic pneumonia who was treated with aureomycin has been omitted.

Clinical Studies—Each patient was observed closely and examined before and at frequent intervals after administration of aureomycin was started until they were well along in convalescence and the common laboratory tests were carried out as indicated. Roentgenograms of the lungs, in addition to those made on admission were repeated as often as feasible, usually twice a week during the hospital stay.

Bacteriologic Studies—Blood cultures were made before treatment was started in every case and were repeated during the next few days when indicated. Fresh sputum specimens were collected before use of aureomycin was started and at frequent intervals thereafter. The patient was required to rinse the mouth and throat thoroughly with water and then to drink a few ounces of tap water. The sputum that was then raised after vigorous coughing was collected in a sterile Petri dish and taken directly to the laboratory. It was then emulsified, streaked on the surface of blood agar plates, planted in blood broth and in many cases also inoculated intraperitoneally into mice. Smears were made and examined in Gram-stained preparations as well as in the fresh state by the Neufeld method. The latter preparations were used not only to identify the types of pneumococci (*Diplococcus pneumoniae*) but also to estimate the numbers of the specific types of pneumococci that were present in the sputum by counting the organisms showing the characteristic capsular swelling in a large number of consecutive oil immersion fields. The blood broth cultures, characteristic colonies from the blood agar plates and the peritoneal exudate and heart's blood cultures of mice were each examined for specific pneumococcus types by the Neufeld method.

² (a) Collins, H. S., Gocke, T. M., and Finland, M. Aureomycin Therapy of Nonpneumonic and Nontuberculous Bacterial Infections, *Arch Int Med* this issue, p. 875. (b) Finland, M., Wells, E. B., Collins, H. S., and Gocke, T. M. Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections, With and Without Pneumonia, *Am J Med*, to be published. (c) Collins, H. S., Wells, E. B., Gocke, T. M., and Finland, M. Treatment of Primary Atypical Pneumonia with Aureomycin, *Am J Med*, to be published.

Tests for Sensitivity to Aureomycin—The various specific types of pneumococci as well as some of the other organisms which grew in abundance in the cultures of the sputum were isolated in pure culture and tested for sensitivity to aureomycin. A serial dilution method in broth or on the surface of aureomycin-containing blood agar plates was used for these tests.³ The aureomycin hydrochloride solutions used for these tests were freshly prepared from the crystalline state each time.

Most of these studies were carried out by Clare Wilcox and Janice M. Bryan. The pneumococcus-typing serums and the aureomycin hydrochloride in sterile vials were provided by the Lederle Laboratories.

Serologic Tests—Blood for the serologic tests was also obtained before and at suitable intervals after the aureomycin treatment was started. The serums were removed after warming the blood to 37 C., and they were then stored in rubber-stoppered pyrex[®] tubes at 5 C. The acute and convalescent phase serums were always tested simultaneously. The following tests were carried out with the serums of most of the patients: tests for cold agglutinins and for Streptococcus MG agglutinins, inhibition of chicken cell agglutination with influenza A (PR8) and B (Lee) viruses and tests for agglutinins for the homologous and for some heterologous types of pneumococci. The methods employed in most of these tests are given elsewhere.^{2c} The antigens used for the pneumococcus agglutinations were saline suspensions of formaldehyde-killed fully grown pneumococcus cultures, some of which were stock preparations that had been kept in a refrigerator for several years and others were freshly prepared from strains isolated from patients in this study. All these tests were carried out by Mildred W. Barnes. The serums of a few of these patients were also tested for complement-fixing antibodies for psittacosis and Q fever, either in the Department of Virus and Rickettsial Diseases of the Army Medical Center, through the courtesy of Dr. Joseph E. Smadel, or in the Division of Viral and Rickettsial Research of the Lederle Laboratories, through the kindness of Dr. Herald R. Cox.

ANALYSIS OF THE CASES STUDIED

Sex and Age (table 1) —There was the usual predominance of males over females. The patients ranged in age from 13 to 75 years, with a preponderance in the older age groups, and 8 of the 33 patients, including 4 with bacteremia, were 65 years of age or older.

Pneumococcus Types —The distribution of the types of pneumococci that were identified is also shown in table 1. Sixteen different types of pneumococci were represented and two thirds of the cases were due to types 1 to 8, exclusive of type 6. It is significant that in 6 of the remaining 11 patients, that is, in the ones having pneumococci of the so-called higher types, the same type was obtained from both blood and sputum. A second type of pneumococcus was identified in the sputum of 2 patients in addition to type 2 pneumococci: type 7 in 1 and type 24 in the other.

Underlying Complications —Some significant underlying complication was present in 18 of the 33 patients, as shown in the lower portion of table 1. Six of the patients had acute alcoholic intoxication when admitted to the hospital, in 3 of these patients delirium tremens

³ Paine, T. F., Jr., Collins, H. S., and Finland, M. Bacteriologic Studies on Aureomycin, J. Bact. **56**: 489-497 (Oct.) 1948.

developed, either before or shortly after treatment with aureomycin was started, and 1 of the latter also had severe cirrhosis of the liver. Evidence of chronic bronchitis and bronchiectasis was made out from the history and the physical and roentgenographic findings in 2 patients, and the patient with bronchial asthma had persistent symptoms during the acute state of the pneumonia and to a milder degree throughout the period of hospitalization.⁴ The patient with rheumatic heart disease had signs of moderate pulmonary congestion and edema on admission to

TABLE 1—*Distribution of Patients by Sex, Age and Pneumococcus Type*

	Number of Patients *
Sex	
Male	20
Female	13
Age	
Under 20 years	4 (2)
20-39 years	9 (2)
40-59 years	12 (3)
60 years and older	8 (4)
Type	
1	6 (3)
2	5 †
3	3
4	2 (1)
5	2
7	3 (1)
12	2 (2)
14	2 (1)
11, 18, 40 (1 each)	3 (3)
8, 19, 20, 31, 33 (1 each)	5
Complicating conditions	
Acute alcoholism	3
Alcoholism and delirium tremens	3
Chronic bronchitis and bronchiectasis	2
Bronchial asthma	1
Cardiac failure (rheumatic)	1
Severe malnutrition	2
Addiction to diacetylmorphine (heroin)	1
Jaundice	2
Agranulocytosis and diabetic acidosis	1
Old cerebral injury	1
Pyelonephritis (K pneumoniae)	1

* The number of those with positive blood cultures is indicated in parentheses

† One had type 7 and another had type 24 pneumococci in the sputums in addition (These are not listed in the table)

the hospital and was promptly digitalized. The jaundice noted in 2 patients was mild (icterus index 12.5 to 20.0) and probably was related to the pneumonia, since it cleared promptly after treatment was started. The patient with agranulocytosis and diabetic acidosis and the one with the old cerebral injury both died, and they will be considered separately later.

Aureomycin Sensitivity of Pneumococcus Strains (table 2)—The sensitivity of the pneumococci obtained from the blood and sputum was

4 This patient, N. G., also had eosinophilia of the blood and sputum; details of this case are presented elsewhere.^{2c}

tested in 30 of the patients. All the strains of the same type of pneumococcus obtained from the blood and sputum before treatment and from subsequent sputum samples when pneumococci could still be isolated had the same sensitivity to aureomycin. The sensitivity of the 32 different strains tested ranged from 0.39 to 3.12 micrograms per cubic centimeter, the majority being completely inhibited by less than 1 microgram per cubic centimeter. A comparison of the sensitivity of these strains with the strain *Streptococcus* 98, which was included as a control in every test, is also shown in table 2. All but 5 of the 32 strains of pneumococci were at least as sensitive as *Streptococcus* 98, and 11 were two or four times as sensitive.

TABLE 2—*Aureomycin Sensitivity of 32 Strains of Pneumococci from 30 Patients*

Sensitivity Mcgm /Cc *	Number of Strains
0.39	7
0.78	13
1.56	7
3.12	5
Comparison with Str. 98 (Control) †	
Four times as sensitive	5
Twice as sensitive	6
Same sensitivity	16
Half as sensitive	4
One fourth as sensitive	1

* Complete inhibition (no growth on subculture) in eighteen hours.

† Sensitivity of *Streptococcus* 98 was 0.78 or 1.56 micrograms per cubic centimeter in different tests.

STATUS OF THE DISEASE AT THE START OF AUREOMYCIN TREATMENT

An analysis of some of the relevant features of the disease in the 33 patients at the time aureomycin treatment was begun is given in table 3. As already noted, none of these patients had previously received any serotherapy, sulfonamides or antibiotics. The first dose of aureomycin was given in most instances on or before the fifth day of illness, and all the patients were acutely ill at the time. Pneumococcemia was demonstrated in the pretreatment blood cultures in one third of the patients. The pulmonary lesion, as judged by physical and roentgenographic indications, was limited to a single lobe in most of the patients, two or three lobes were involved in 9 patients, and in only 4 of the latter was the lesion bilateral.

All the patients were febrile when aureomycin treatment was started, and the temperature at that time was below 101° F. in only 1 of them. In the majority, the temperature was 103° F. or higher, and in 3 patients

it was over 105 F. The leukocyte counts ranged from 2,200 to 33,700 per cubic millimeter, with totals below 10,000 in 4 and over 25,000 in 6. An attempt was also made to arrive at a general estimate of the severity of the illness in each patient from all the observations made at the time aureomycin therapy was undertaken. Most of the patients were considered to be moderately or severely ill. In only 2 patients was the illness judged to be mild, and 1 patient was almost moribund at the time

TABLE 3—*Status of 33 Patients with Pneumococcic Pneumonia at the Start of Aureomycin Treatment*

Findings	Number of Patients
Day of disease	
1	4
2	3
3	6
4	11
5	4
6-14	5
Blood culture	
Positive	11
Negative	22
Pulmonary involvement	
1 lobe	24
2 lobes (unilateral)	5
2 or 3 lobes (bilateral)	4
Temperature F	
100.4-101.9	7
102.0-102.9	9
103.0-103.9	9
104.0 or higher	10
Leukocyte count	
Less than 10,000	4
10,000-14,000	11
15,000-19,000	8
20,000-24,000	4
25,000 or more	6
Estimated clinical severity	
Mild	2
Moderate	18
Severe	12
Critical	1

DOSAGE

An analysis of the dosage of aureomycin used for the 33 patients with pneumococcic pneumonia is given in table 4. Most of the patients received all the aureomycin by mouth in doses varying from 1.0 Gm every four or six hours to 0.5 Gm given at intervals of four, six or eight hours. In 9 of the 16 patients who received individual doses of 1.0 Gm, these were reduced to 0.5 Gm after the temperature reached normal and the condition had improved.

The total oral dose of aureomycin ranged from 5.5 to 46.5 Gm given over a period ranging from two to fifteen days. Most of the patients received less than 20 Gm and were treated for five days or less. The

average dose for the 27 patients who were treated orally was 17.7 Gm given over an average of about five and one-half days

Parenteral therapy was used in the treatment of 6 patients. Two of these patients received repeated doses of 100 mg each, some given intravenously and the rest intramuscularly at intervals of two to four hours. In these cases, each dose was given in 10 cc of 0.7 per cent sodium carbonate solution, and the intravenous doses were given very slowly, ten to fifteen minutes being taken for each injection. Both of these patients died: one after receiving only five doses in fourteen hours and the other after six doses had been given in fourteen hours.

TABLE 4—*Analysis of Dosage*

	Number of Patients
Dosage started by mouth	
1.0 Gm every 4 hours	8
1.0 Gm every 6 hours	8
0.5 Gm every 4 hours	5
0.5 Gm every 6 hours	4
0.5 Gm every 8 hours	2*
Total oral dose	
Less than 10 Gm	4
10 to 19 Gm	14
20 to 29 Gm	6
30 Gm or more	3
Average (27 patients)	17.7 Gm
Total duration of oral therapy	
2 or 3 days	4
4 or 5 days	13
6 or 7 days	5
8 days or longer	5
Average (27 patients)	5.6 days
Parenteral therapy only	
Intravenous and intramuscular	
100 mg every 2 to 4 hours	2
Average total dose	550 mg
Intravenous only	
500 mg once daily †	4
Average total dose	2.05 Gm

* One of these patients received several doses of 100 mg intramuscularly every four hours before the first oral dose.

† One patient received an initial dose of 750 mg, in another patient oral aureomycin was given during convalescence for underlying chronic bronchopulmonary infection.

Four other patients received aureomycin for their pneumonia only by the intravenous route. The individual doses for these 4 patients consisted of 500 mg of crystalline aureomycin hydrochloride given in 1.0 or 1.5 liters of either isotonic sodium chloride solution or 5 per cent dextrose solution in distilled water. These were given once daily by slow drip, taking about an hour or longer for each injection. The initial dose for 1 patient was 750 mg given in the same manner. No special buffers were used with these injections, and the reaction of the final solutions was about p_H 3.5 to 4.0. The average total dose for these 4 patients was 2.05 Gm, and the interval between the first and the last dose averaged seventy-two hours.

Two of the patients received penicillin in addition to aureomycin, one of them was the patient with agranulocytosis who died, and the other received the penicillin only during convalescence. No other antimicrobial agents were used for any of the remaining patients.

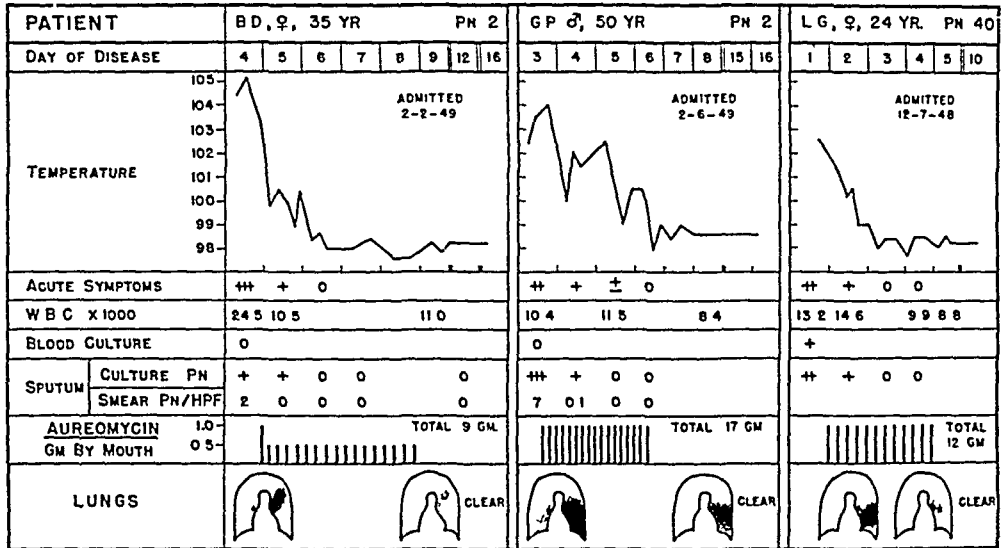


Chart 1—Significant data on 3 patients with pneumococic pneumonia who were treated with aureomycin by mouth

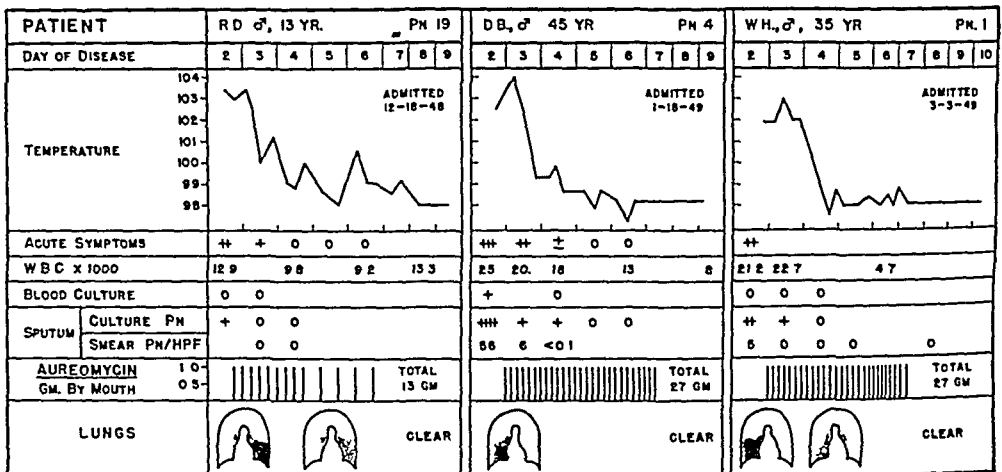


Chart 2—Course and other significant data in cases of 3 additional patients with pneumococic pneumonia treated with aureomycin by mouth

RESULTS OF AUREOMYCIN THERAPY

The general effects of aureomycin by mouth on the clinical course and bacteriologic observations in the first 4 patients of this series have been noted briefly in a preliminary communication⁵. These effects as

⁵ Collins, H. S., Paine, T. F., Jr., and Finland, M. Aureomycin in Treatment of Pneumococcal Pneumonia and Meningococcemia, *Proc Soc Exper Biol & Med* 69:263-265 (Nov) 1948

observed in 6 other cases of moderate severity are illustrated graphically in charts 1 and 2. The course and relevant data on 3 additional patients, who were each over 65 years old and bacteremic and, therefore, may be considered as having a very grave prognosis,⁶ are shown in chart 3. Two patients died within eighteen hours of the time aureomycin treatment was started, and the salient features of these cases will be considered separately. An analysis of the effects of aureomycin on the clinical course of the 31 patients who recovered is presented in table 5. The 4 patients who were given the aureomycin by the intravenous route

TABLE 5—*Effect of Aureomycin on the Clinical Course in 31 Patients with Pneumococcic Pneumonia*

	Number of Patients
A First major sustained drop in temperature	
Less than 12 hours	10
12-23 hours	15
24-35 hours	3
36-47 hours	3
B Total duration of temperature over 99.2 F	
Less than 24 hours	12
24-47 hours	11
48-71 hours	3
72 hours or longer	5
C Major sustained improvement in symptoms	
12 hours or less	12
13-24 hours	13
25-48 hours	6
D Essentially complete symptomatic improvement	
Less than 24 hours	7
24-47 hours	16
3 or 4 days	5
More than 4 days	3
E Definite clearing of pulmonary lesion as determined by physical examination or by roentgenograms	
2-4 days	13
5-6 days	9
7-8 days	6
9 or more days	3
F Lungs entirely clear by physical examination, roentgenograms or both	
7 days or less	17
8-14 days	11
More than 14 days	3

are also included in this analysis. The data on 3 of these patients are shown in chart 4.

Effect on Fever—There was a marked drop in temperature during the first two days after the administration of aureomycin was started in all 31 patients who recovered. In all but 6 of these patients the major reduction in the fever had occurred within the first twelve or twenty-four hours. There were only 8 patients in whom any fever persisted or recurred after the second day, and in these patients the temperature did not usually exceed 100 F after that time. Three of these patients became afebrile during the third day, and in 2 others the temperature remained normal after the fourth day.

⁶ Tilghman, R. C., and Finland, M. Clinical Significance of Bacteremia in Pneumococcic Pneumonia, *Arch Int Med* 56: 602-619 (April) 1937.

Of the 3 patients whose fever persisted for longer than four days, 1 had delirium tremens and in him a sterile pleural effusion also developed. The course of this patient, J A, is shown in chart 5. In a second patient the fever was associated with a persistent leukocytosis, but the patient had no localizing signs or symptoms of any complication.

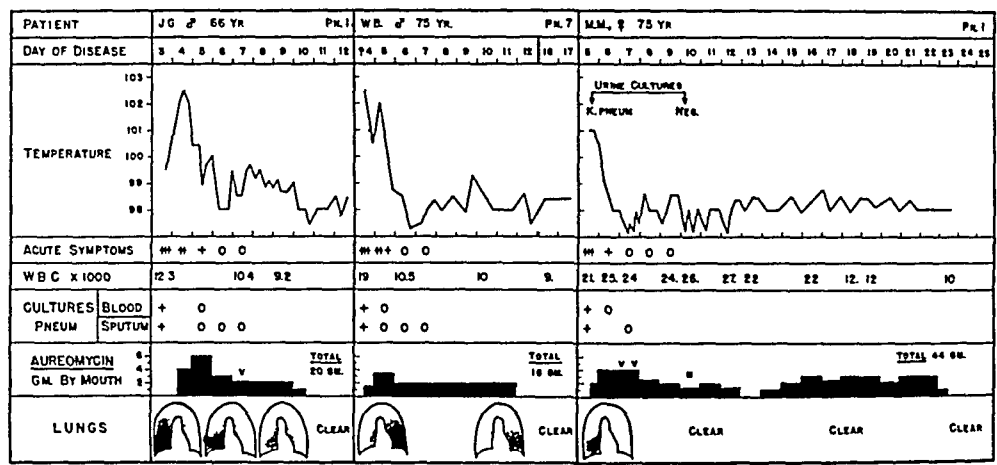


Chart 3—Data on 3 bacteremic patients over 65 years of age with pneumococcic pneumonia treated with aureomycin by mouth

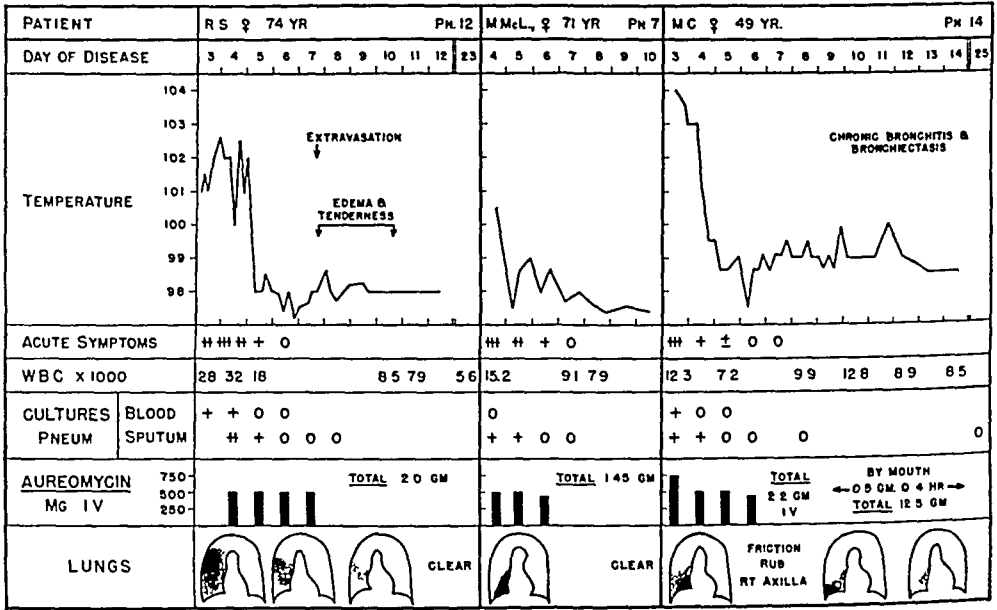


Chart 4—Course and significant data in cases of 3 patients with pneumococcic pneumonia treated with aureomycin intravenously

and the lesion in the lung was clearing rapidly during this time. The fever subsided while the aureomycin was still being given, and test doses of aureomycin subsequently failed to reproduce the fever, hence the fever cannot definitely be ascribed to the antibiotic. The data on this patient, M McC, are shown in chart 6. In the third patient, the pneu-

monia began during a severe attack of influenza A, and treatment, which was started with intramuscular doses, resulted in a slow but steady deferescence of fever, which cleared only after oral therapy was given. The

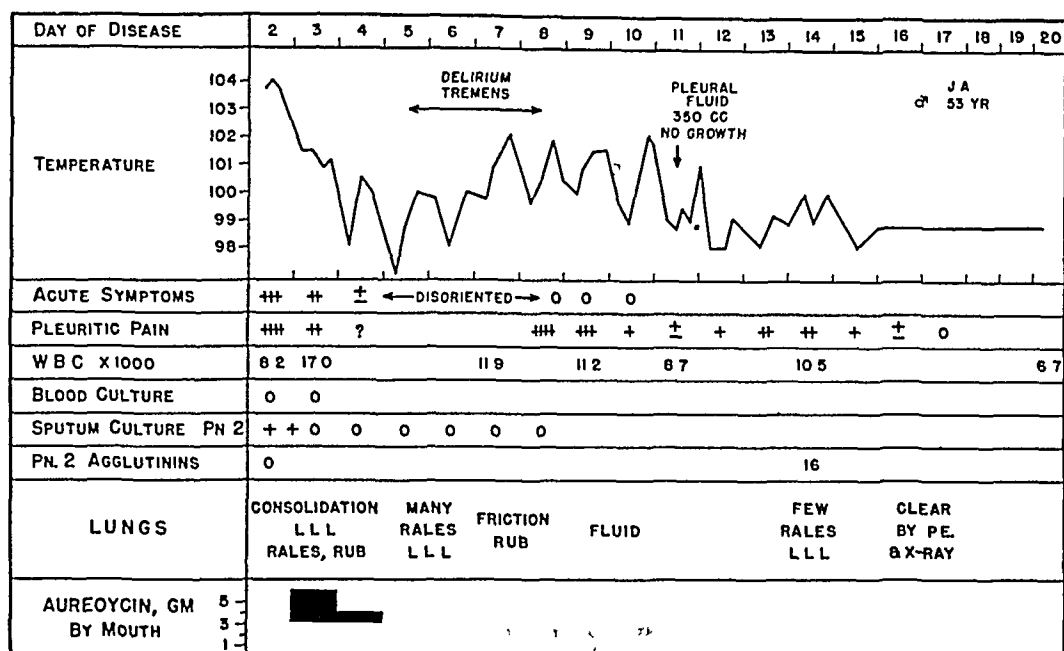


Chart 5—Course and significant data in the case of a patient with type 2 pneumococcus pneumonia treated with aureomycin by mouth

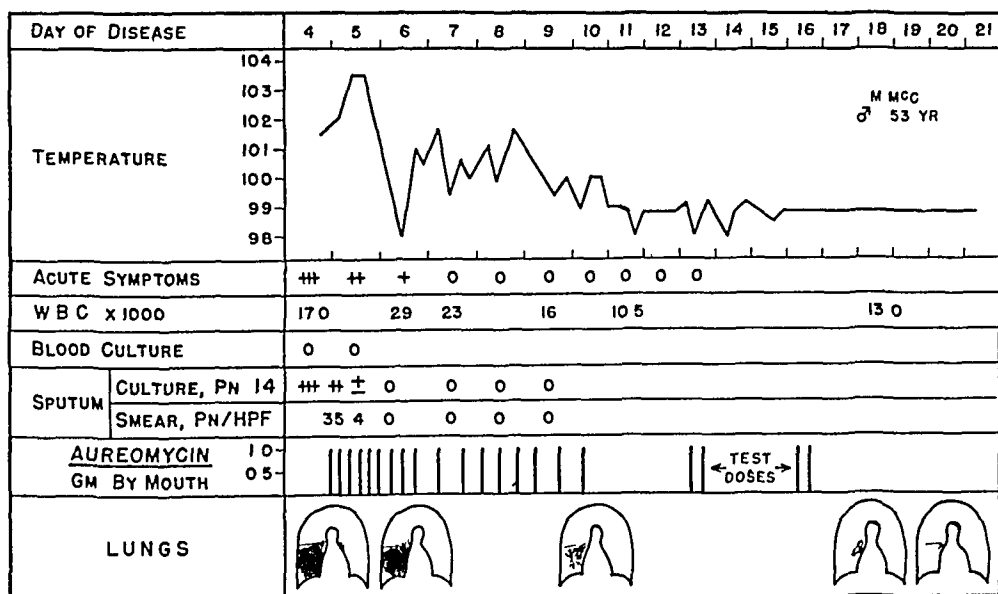


Chart 6—Persistent fever and leukocytosis in the case of a patient with type 14 pneumococcus pneumonia treated with aureomycin by mouth

course and findings in the case of this patient, G G, have been presented elsewhere^{2c}

Effect on Symptoms—Improvement in the acute symptoms of the pneumonia usually paralleled the drop in temperature. In some

patients the subjective improvement actually preceded by several hours the major drop in temperature, and only an occasional patient continued to appear acutely ill for any length of time after the temperature had dropped to a nearly normal level. There were 5 patients who continued to have minor symptoms during the third and fourth day after treatment was begun but only 3 continued to have significant symptoms of acute illness after the fourth day.

One of the latter was patient J. A. who had the pleural effusion. The second patient (M. C., chart 4) received intravenous therapy at first and showed marked improvement. There was some persistence of pleural pain, cough and expectoration, and roentgenograms suggested the presence of fluid, but the signs and symptoms cleared after oral administration of aureomycin was instituted. The third patient was the one who had bronchial asthma, she continued to have some respiratory distress and wheezing after her fever and other acute symptoms had subsided.

Effect on the Pulmonary Lesion—The lungs, in general, cleared rapidly after aureomycin therapy was started, as indicated in sections E and F in table 5. Definite and usually marked clearing was evident from the physical signs and roentgen observations within six days after treatment was started in more than two thirds of the patients who recovered. Signs of consolidation or fluid persisted over most of the affected area for more than eight days in only 3 patients.

With the exception of these 3 patients, complete clearing was demonstrated in roentgenograms taken on or before the end of the second week after the aureomycin treatment was initiated. In several patients, moreover, the last roentgenogram which still showed pulmonary infiltrations to be present had been taken from four to eight days earlier, and in most of them the pulmonary lesions had already largely cleared at that time. The 3 patients whose lesions persisted longer than two weeks were also the ones whose symptoms persisted the longest.

EFFECT OF AUREOMYCIN ON THE BACTERIOLOGIC FLORA

Effect on Bacteremia—Pneumococci were obtained from the pre-treatment blood cultures in 11 patients, but only one of the blood cultures taken after treatment was started was positive. This culture was obtained nine hours after the first parenteral dose of aureomycin was given to the patient with agranulocytosis, and the next culture, taken three hours later, showed no growth.

Effect on the Pneumococci in the Sputum—Attempts were made to identify and isolate pneumococci from the sputum in all of the patients before and at frequent intervals after aureomycin treatment was started. The results of the sputum studies are summarized in table 6. In 11

patients, including 4 with bacteremia, the only specimens of sputum which yielded pneumococci were those obtained before the first dose of aureomycin. The first specimen in which pneumococci could not be identified either in direct smears or by the various cultural methods was obtained eight to twelve hours after the first dose in 4 of these 11 patients, within the first twenty-four hours in 5 others and within thirty-six hours after treatment was begun in the remaining 2. There were only 2 patients in the entire series in whom pneumococci were still demonstrable in sputum more than thirty-six hours after treatment was started, the longest interval being fifty-nine hours. It is thus seen that not only the pneumococcemia was promptly cleared but the pneumococci were rapidly eliminated from the sputum after the aureomycin treatment was started.

TABLE 6—*Effect of Aureomycin on the Persistence of Pneumococci in the Sputum*

Interval After Start of Aureomycin Therapy	Number of Patients *
A Last sputum in which pneumococci were demonstrated	
Pretreatment only	11 (4)
Less than 12 hours	9†(2)
12-23 hours	8 (3)
24-35 hours	3 (1)
36-47 hours	1 (1)‡
48-59 hours	1
B First sputum in which pneumococci could no longer be demonstrated	
Less than 12 hours	4 (1)
12-23 hours	10 (6)§
24-35 hours	9 (1)
36-47 hours	5 (1)
48-59 hours	3 (1)
60-86 hours	2 (1)

* Two of the patients are listed twice (once for each type of pneumococcus). The parentheses indicate the number with bacteremia.

† One of these patients died before further specimens were obtained.

‡ No further sputum was available in this patient.

§ One fatal case is included in this figure.

Most of the strains of pneumococci isolated from sputum during or after the aureomycin treatment were tested for sensitivity to the antibiotic simultaneously with the corresponding pretreatment strains that had been isolated from both sputum and blood of the same patients. All strains of the same type obtained from the same patient were found to have identical sensitivity to aureomycin.

Results of Intravenous Therapy—In the 4 patients who were treated with daily intravenous injections, the effects on the acute disease and on the bacteriologic findings were quite similar to those observed in the patients who received larger and more frequent doses by mouth. The major drop in temperature and symptomatic improvement occurred in each of these patients before the second dose was given. The optimum dose by the intravenous route has not been determined. The course and

relevant data in the cases of 3 of these 4 patients, including the only one of the 4 who later received aureomycin orally, are shown in chart 4. The oral therapy was given to this patient after the acute symptoms had been entirely relieved, in an attempt to influence an underlying chronic bronchopulmonary infection and a suspected pleural effusion.

REPORT OF FATAL CASES

In both of the fatal cases, all the aureomycin was given parenterally and death occurred within eighteen hours after the first dose was given. The salient features of these 2 cases may be summarized briefly.

The first patient was a 53 year old white man, known to have diabetes of long standing, who had been taking insulin regularly. The only history pertaining to the immediate illness that was obtainable at the time of admission was that the patient had been vomiting and coughing for three days, complained of bilateral pleuritic pain and was raising brownish sputum for two days. On the day before entry he was unable to work and a physician found his temperature to be 103 F. When first seen, he appeared extremely ill, semistuporous, markedly dehydrated, dyspneic and cyanotic. His temperature was 104 F, pulse rate 150, respiration rate 45 and blood pressure 70 systolic and 50 diastolic. Consolidation of the lower two thirds of the right lung was made out by physical examination and verified by roentgenograms. The blood sugar was 318 mg per hundred cubic centimeters, carbon dioxide content 34 volumes per cent and serum chlorides 91 milliequivalents per liter, and the urine gave a positive reaction for sugar and showed a trace of acetone. The white blood cell count was 2,200, of which 55 per cent were polymorphonuclears, all of them "extremely toxic."

Aureomycin was given in 100 mg doses parenterally, each in 10 cc of dilute sodium carbonate buffer at about three hour intervals, a total of five doses were given, three of them intravenously and the third and the last doses intramuscularly, all without any untoward effects. At the time of the last two doses, the patient was also given penicillin, 200,000 units intravenously with one and 500,000 units intramuscularly with the other. He was also treated vigorously for his diabetes with insulin and parenteral fluids. A second leukocyte count, made a few hours after entry, showed 1,200 cells, and the smear showed no granulocytes. There was no improvement in the patient's general condition, and he died about eighteen hours after the first dose of aureomycin.

Blood cultures taken on admission and again before the first and third doses of aureomycin all showed type 11 pneumococci. A fourth culture of the blood taken before the first dose of penicillin showed no growth, and culture of the cardiac blood taken at autopsy showed only *Aerobacter aerogenes* and no pneumococci. Sputum was not obtainable, and pharyngeal cultures made before treatment showed type 11 pneumococci in abundance and a few colonies of *Staphylococcus aureus*. A second throat culture, made ten hours later, showed only two colonies of type 11 pneumococci, a few colonies of *Staph aureus* and of *Hemophilus influenzae* and a single colony of *A. aerogenes*. Each of the cultures made of materials aspirated from all parts of the lung at the time of death, and those made from all lobes of the lungs at autopsy yielded a heavy growth of *A. aerogenes* in almost pure culture. No pneumococci could be identified, either directly by the Neufeld reaction or in the cultures from any of the autopsy materials. The strains of *A. aerogenes* from the various cultures were all completely inhibited

by aureomycin in concentration of 125 micrograms per cubic centimeter, the staphylococci and *H. influenzae* were both inhibited by 312 micrograms per cubic centimeter and the pneumococci were all sensitive to 0.78 micrograms per cubic centimeter.

In the second patient, a 21 year old Negro, the acute illness, which was preceded by mild coryza and cough, began with a shaking chill two days prior to admission to the hospital. This was followed by fever, an increase in cough, which became productive of blood-tinged sputum, and pleuritic pain, which was localized in the left upper anterior part of the chest. The only significant history of other illness was that of a head injury eight years previously after which he was unconscious for some time and then was left with a hemianopsia lasting two months. Since that time he had had several recurrences of hemianopsia, each lasting a few days and induced by jarring of the head. He was acutely but not critically ill and had signs of consolidation limited to the lower lobe of the left lung. The temperature was 104.5 F, pulse rate 112, respiration rate 40 and blood pressure 100 systolic and 64 diastolic. The white blood cell count was 9,100, of which 92 per cent were polymorphonuclears, most of them young forms. *Pneumococcus* type 1 was identified directly in the sputum, and the blood culture showed no growth.

Aureomycin was given in 100 mg doses as in the previous case, beginning with one intravenous and one intramuscular injection and followed at two to four hour intervals by three intramuscular injections and a final one given intravenously because of the local soreness at the sites of the previous injections. There were no other untoward effects noted, and the patient appeared to improve rapidly. After the last injection the patient was cheerful, did not appear "toxic," ate his evening meal and enjoyed a visit from his friends. He was later found dead in bed, without evidence of antecedent activity, three hours after the last dose and seventeen hours after the first dose of aureomycin. Only twenty minutes previously he had chatted with a ward attendant, who had brought him a urinal, which he had used without incident. The cause of death was not determined, as permission for autopsy was denied.

The first patient was obviously in a critical condition when aureomycin treatment was started. Granulocytopenia, and shortly thereafter agranulocytosis, was demonstrated and presumably was the result of severe infection, although it may have been due to some other unexplained cause. The diabetic acidosis, though not severe, was not readily controlled. The pneumococci in this case were rapidly eliminated and could no longer be demonstrated at the time the first dose of penicillin was given, but *A. aerogenes* rapidly invaded the lungs and the blood.

The death in the second case remains unexplained and occurred after the patient was showing favorable progress similar to that noted in all the other patients following aureomycin therapy. The possibility of some episode related to his previous cerebral injury cannot be eliminated, but it did not produce any obvious manifestations. Furthermore, there was no indication of any untoward reactions from the aureomycin injections other than the local pain and tenderness from the

intramuscular injections in either of these 2 patients or in any of a large number of other patients who received similar parenteral injections for various conditions

COMPLICATIONS

The only complications of the pneumonia noted in any of the patients who recovered have already been referred to in other connections. A sterile pleural effusion was demonstrated in 1 patient (J A, chart 5) and was suspected but could not be demonstrated in another (M C, chart 4), and an unexplained episode of fever and leukocytosis without symptoms followed apparent recovery in a third patient (M McC, chart 6)

TOXIC EFFECTS OF AUREOMYCIN

The only significant untoward effects that resulted from oral aureomycin therapy were those referable to the gastrointestinal tract. Only 6 of these patients had nausea and vomiting, however, this was not sufficient to interfere with therapy although the dose was reduced in some instances. Seven patients, including 5 of those who had some vomiting, passed large and bulky stools, usually two or four a day, which only occasionally became watery. In 19 patients there were no untoward effects from the oral preparations used. It is of interest that the gastrointestinal symptoms seemed to be much less frequent in the present series of patients than they were in those who were treated with aureomycin orally for primary atypical pneumonia,^{2c} but this may be only coincidental.

The intramuscular doses were accompanied with moderate pain that lasted for about half an hour, and there was residual local tenderness for several hours. In 1 of the 4 patients receiving the large intravenous doses there was extravasation of some of the solution of aureomycin at the time of the fourth injection and this resulted in some redness, tenderness and swelling along the course of the vein for several inches and later there was slight edema of the forearm. This all cleared in a few days.

There were no instances of fever or rash and no evidence of toxic effects on the blood, kidneys, liver or nervous system attributable to either the orally or the parenterally administered aureomycin in any of the patients.

RESULTS OF SEROLOGIC TESTS

Agglutination tests with antigens prepared from homologous and heterologous types of pneumococci were carried out in the acute and convalescent phase serums of 20 patients. Agglutinins for pneumococci of the homologous types were demonstrated in titers ranging from 1:2 to 1:16 in the convalescent phase serums of 11 of these patients, including 5 who had positive blood cultures. The other 10 patients in whose

serums agglutinins could not be demonstrated included 3 who had pneumococcemia. However, the agglutination test, as used here, is not a very sensitive one for the demonstration of pneumococcus antibodies.⁷

Tests for cold agglutinins, *Streptococcus* MG agglutinins and anti-influenza A and B hemagglutinins were carried out in 26 of the patients. Cold agglutinins developed in low titer in 1 patient, G G, and were present in high titer in both acute and convalescent phase serums in another. The latter was the patient N G, who had asthma. Some of the details of both of these cases have been presented elsewhere.^{2c} No significant titers or rises in titer of agglutinins for *Streptococcus* MG were found in any of the patients. A significant rise in titer of antibodies for influenza A was demonstrated in 3 patients, including G G, in whom cold agglutinins also developed. The illness in these 3 patients occurred during the latter half of March 1949, when influenza A was prevalent in this community.

COMMENT

The present study was part of a general investigation of the range of effectiveness of aureomycin in acute pneumonias of diverse origin. The cases presented in this paper form a fairly uniform etiologic group, perhaps more so than any of the other prevalent types of pneumonia. They were, therefore, particularly suitable for a therapeutic evaluation. To be sure, the sulfonamides, and more particularly penicillin, have already proved to be highly effective in such cases, and rarely does the latter fail to bring about a cure in uncomplicated cases of this disease. It was, nevertheless, of interest to include the pneumococcic pneumonias in any general test of the therapeutic range of an effective antibiotic, and it seemed all the more justified after the initial favorable results were demonstrated.

The clinical and laboratory data that have been presented indicate clearly that aureomycin given either orally or intravenously is highly effective in the treatment of pneumococcic pneumonia. The results in the individual cases were quite decisive, and the beneficial effects were demonstrated with great regularity in all patients. The bacteriologic findings with respect to the disappearance of pneumococci from the sputum appear to be even more impressive than the results of similar

7 (a) Finland, M., Sping, W. C., Jr., and Lowell, F. C. Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, *J Clin Investigation* **19** 179-199 (Jan.) 1940. (b) Finland, M., Strauss, E., and Peterson, O. L. Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole, *Ann Int Med* **16** 1-16 (Jan.) 1942. (c) Winkler, A. W., and Finland, M. Antibody Response to Infections with the Newly Classified Types of Pneumococci (Cooper), *J Clin Investigation* **13** 109-120 (Jan.) 1934.

studies in patients treated with sulfonamides⁸ or with penicillin⁹ Furthermore, in the present cases the effectiveness of aureomycin did not seem to be dependent on the stage of the disease when the antibiotic was given and no suppurative pneumococcal complications developed There were no cases, however, in which such suppurative complications were already present at the time when the aureomycin was started In the 2 fatal cases the deaths were not the result of any failure to influence the pneumococcal infections

Although penicillin treatment was not given in any parallel and comparable cases in this study, results in the present cases may be considered entirely comparable to those which have been observed here and elsewhere in similar patients treated with adequate doses of penicillin The latter antibiotic may have the advantage of simplicity of administration, generally lower toxicity and, for the present at least, lower cost Aureomycin, nevertheless, may prove advantageous under certain circumstances, particularly in cases of mixed etiology, in which the pneumococcus is only one of the causative agents, or in patients who are sensitive to penicillin or possibly in a rare case, if there be such, in which the causative pneumococcus is relatively resistant to penicillin Further studies on the effect of aureomycin in patients with suppurative complications should also be of interest, but such cases were not available during the course of this study

CONCLUSIONS

The clinical and laboratory data which have been presented indicate that aureomycin hydrochloride given either by mouth or intravenously is highly effective in the treatment of pneumococcal pneumonia

8 Goodwin, R. A., Jr., Wilcox, C., and Finland, M. Persistence of Pneumococci in Sulfonamide Treated Case of Pneumonia, *Am J M Sc* **209** 628-639 (May) 1945

9 Ory, E. M., Harris, H. W., Meads, M., Wilcox, C., and Finland, M. Bacteriologic Studies of the Sputum in Patients with Pneumococcal Pneumonia Treated with Penicillin, *J Lab & Clin Med* **31** 409-422 (April) 1946

AUREOMYCIN THERAPY OF NONPNEUMOCOCCIC AND NONTUBERCULOUS BACTERIAL PULMONARY INFECTIONS

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THE RANGE of activity of aureomycin includes a wider variety of the known causative agents of pneumonia than that of any of the earlier effective chemicals or antibiotics¹ Clinical trials were, therefore, undertaken of the use of aureomycin in all types of nontuberculous pneumonia and other severe acute infections of the respiratory tract that were available for study In separate communications, we have presented the results of aureomycin treatment in cases of primary atypical (virus) pneumonia,² in cases of pneumococcic pneumonias³ and in a variety of other cases which includes influenza and other severe acute infections of the respiratory tract and pneumonias in which a likely causative bacterial agent could not be identified⁴ In this paper are presented the results of aureomycin therapy in cases of the nonpneumococcic and nontuberculous bacterial infections of the lungs

MATERIALS AND METHODS

Selection of Cases—Two groups of cases were studied and treated Group I includes 13 patients with acute pneumonia in whom cultures of sputum obtained before any therapy was given yielded predominant or pure growths of pathogenic

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1 Duggar, B M, and others Aureomycin A New Antibiotic, *Ann New York Acad Sc* **51** 175-342 (Nov 30) 1948

2 Collins, H S, Wells, E B, Gocke, T M, and Finland, M Treatment of Primary Atypical Pneumonia with Aureomycin, *Am J Med*, to be published

3 Gocke, T M, Collins, H S, and Finland, M Aureomycin Treatment of Pneumococcic Pneumonia Clinical and Laboratory Studies on Thirty-Three Patients, *Arch Int Med*, this issue, p 857

4 Finland, M, Wells, E B, Collins, H S, and Gocke, T M Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections, With and Without Pneumonia, *Am J Med*, to be published

bacteria other than pneumococci. Most of these patients had an antecedent illness which was consistent with the diagnosis of "clinical influenza" and which occurred during March 1949, when proved influenza virus infections were prevalent in this community. None of these patients had received any antimicrobial agents before the administration of aureomycin was started, and they were acutely ill, with physical and roentgen signs of pneumonia at the time. Four of these patients were treated in nearby hospitals, and the others were from the medical wards of the Boston City Hospital. Group II includes 20 patients with infections that can best be characterized as "nontuberculous bronchopulmonary suppuration." These patients were all from the adult medical wards of the Boston City Hospital. All but 1 of them had been treated with large doses of other antimicrobial agents for varying periods before aureomycin therapy was started and had obtained only temporary benefit or none at all from the previous therapy. They were all acutely ill, some of them were also chronically ill, and all but 5 were febrile at the time aureomycin was started. In each case, pathogenic bacteria other than pneumococci were obtained in abundance or in pure growth from cultures of the sputum before the use of aureomycin was started.

Bacteriologic Studies—Blood cultures were made just before aureomycin therapy was initiated and at irregular intervals during its administration. Stained smears and aerobic cultures were also made from carefully collected and freshly raised sputum before and at intervals during and after the aureomycin therapy. The predominant organisms were isolated in pure culture and tested for sensitivity to aureomycin by a serial dilution method either in suitable liquid mediums or on the surface of suitable agar mediums containing aureomycin.⁵ Some of the cultures were done in the bacteriologic laboratory of the Mallory Institute of Pathology by Marion E. Lamb and A. Kathleen Daly, most of the sputum cultures and all the tests for aureomycin sensitivity were done by Janice M. Bryan and Clare Wilcox.

Serologic Tests—Blood for serologic tests was obtained before and at suitable intervals after administration of aureomycin was started in all of the patients of group I and in some of those in group II. Tests for cold agglutinins, Streptococcus MG agglutinins and antihemagglutinins for the PR8 strain of influenza A and the Lee strain of influenza B organisms were done in all serums by the same methods as those used in the other collateral studies.² These tests were carried out by Mildred W. Barnes.

Dosage—Almost all the aureomycin was given by mouth in the form of capsules, each containing 250 mg of the crystalline hydrochloride, but occasional patients received some or all of the oral doses of the antibiotic in the form of the aureomycin base. One patient (case 15) received only intravenous injections of aureomycin hydrochloride, 500 mg daily in 1,000 or 1,500 cc of a 5 per cent solution of dextrose in water, and a second patient (case 7) received similar therapy for four days, after which he was treated orally. The dosage used to initiate the oral therapy in the patients of both groups was as follows:

Starting Dosage	Number of Patients	
	Group I	Group II
10 Gm every 4 hours	5	11
10 Gm every 6 hours	4	3
0.5 Gm every 4 hours	2	6
0.5 Gm every 6 hours	2	

5 Paine, T. F., Jr., Collins, H. S., and Finland, M. Bacteriologic Studies on Aureomycin, *J. Bact.* 56:489-497 (Oct.) 1948.

This dosage was later revised in many instances, the larger doses being reduced after the patient improved or if there was intense vomiting and the smaller doses increased if the patient did not improve promptly

All the aureomycin was provided by the Lederle Laboratories, Division American Cyanamid Company, through the courtesy of Dr Stanton M Hardy

ACUTE BACTERIAL (NONPNEUMOCOCCIC) PNEUMONIA

Some of the relevant clinical and laboratory findings in the 13 cases of acute bacterial pneumonia are listed in table 1. The patients were mostly young adults, but 4 of them were 60 to 76 years old, 8 of the 13 were men. The predominant organism isolated from the pretreatment sputum was either a beta hemolytic streptococcus, hemolytic *Staphylococcus aureus* or both in 11 of the patients, a hemolytic streptococcus and *Klebsiella pneumoniae* (Friedlander's bacillus) type A in 1 patient and *Hemophilus influenzae* in another. All the blood cultures taken in these cases yielded no growth.

Relation of the Pneumonia to Influenza Virus Infections—There was evidence of the prevalence of influenza virus infection (mostly influenza A) in this community during the month of February and March 1949, most of the cases occurring during the latter month. The onset of the pneumonia in the present group of patients occurred during March 1949 in 9 cases (1 to 6, 8, 10 and 11), in April in 2 (7 and 9), in June 1949 in 1 (case 12) and in December 1948 in 1 (case 13). Except in the last 2 cases there was a history of antecedent systemic symptoms and symptoms referable to the upper respiratory tract compatible with a diagnosis of clinical influenza. This illness began from one to six days before the time of onset of the symptoms of pneumonia in cases 1 to 5 and from one to four weeks earlier in the remaining cases, the longest interval being in the cases in which pneumonic symptoms began during April.

Tests for hemagglutinin inhibition of influenza A and B organisms were made on the serums obtained during the acute and convalescent phase of the pneumonia in 12 of the 13 patients. The results are shown in table 1. There was conclusive evidence of influenza B infection in case 1 as indicated by a marked rise in titer of antibodies for the Lee strain and by the isolation of a strain of influenza B virus from the washing from the throat. In cases 2, 3, 4 and 5 there was serologic evidence of influenza A infection which, in case 2 was confirmed by the isolation of a strain of influenza A virus from the garglings obtained at the time of admission to the hospital. Elevated titers strongly suggestive of recent infection with influenza A virus were found during the acute stage of the pneumonia in cases 6, 9 and 10 and a significantly elevated titer of anti-influenza B hemagglutinins was found in case 7. Slightly elevated titers that may represent recent infection with influenza B

TABLE 1—*Relevant Data on 13 Patients with Acute Bacterial (Nonpneumococcal) Pneumonia Treated with Aureomycin*

Case	Sex	Age	Predominant Organisms in Sputum	Condition When Aureomycin Therapy Was Begun										Effect on the Course of the Disease				
				Anti Influenza Hemagglutinins		Day of Dis ease	Temp, °F.	White Blood Cells	Pulmonary Lesions		Estimated Severity	Aureomycin, Total Dose		Drop in Symp toms		Lungs Cleared, Days	Esti mated Benefit	
				A (PRS)	B (Lee)				Type	Lobes		Gm	Days	Im proved, Hr	Days			
1	F	14	Str β_2 , Staph aureus ₂	32/32	S*/2048	3	103.4	10,400	B	Rml, Ll	Severe	71.5	18	37 days	27 days	9 16†	Good	
2	M	72	Str β_2 , K pneumoniae _{1a}	S*/256	8/8	4	103.0	10,800	B	Rum	Severe	20.0	5½	12.24	12.24	3 14†	Excellent	
3	M	15	Str β	16/128	8/4	5	103.2	4,300	B	Lu	Moderate	14.5	4	12.24	12.24	2.5	Excellent	
4	F	23	H influenzae	128/256	4/4	3	103.8	15,300	B	Rl	Moderate	10.0	2½	12.48	12.48	3.7	Good	
5	M	21	Str β	8/32	16/16	6	105.0	9,000	B	Ll	Moderate	16.0	5	12.18	24.72	3.5	Good	
6	F	34	Str β_2	64/64	8/8	2	105.0	16,100	L	Rml	Severe	17.0	5	21	24.48	7 14	Good	
7	M	64	Str β_{12} , Staph aureus ₃	0/0	128/64	1	101.0	9,800	I	Il	Moderate	24+15	7	12.06	1.6 days	3.7	Good ?	
8	F	22	Staph aureus	0/0	32/32	4	105.0	8,900	B	Il	Moderate	8.0	3	12.36	24	4.7	Excellent	
9	M	15	Staph aureus	128/128	16/16	2	102.0	11,700	I	Ll	Moderate	9.0	1½	12	12.24	2.5	Excellent	
10	F	76	Str β	256/128	4/4	3	101.0	11,500	B	Rl	Mild	6.0	2	18.24	12.24	4	Good ?	
11	M	42	Str β_2 , Staph aureus ₂			2	104.0	15,800	B	Rl	Severe	24.0	4½	12	12.24	4.5	Excellent	
12	M	17	Str β_2	8/8	32/32	7	103.4	11,800	I	Ll	Moderate	9.5	5	12.48	18.36	2.5	Excellent	
13	M	60	Str β_1 , Staph aureus ₃	16/6	4/4	2	105.0	14,500	B	Rl	Severe	11.0	5½	24.48	24.48	3.4	Excellent	

Explanations and abbreviations. Subscripts indicate aureomycin sensitivity in micrograms per cubic centimeter (complete inhibition). Anti influenza hemagglutinins. The titers are given (acute/convalescent) as the reciprocal of the highest final dilution of serum 0 = <1. * homologous virus isolated at this time. Day of disease refers to onset of pneumonia, antecedent influenza, or other acute respiratory disease begun at about the same time in cases 1, 2, 3, and 13-6 and 3 days earlier, respectively, in cases 4 and 5 and from one to four weeks earlier in the other cases. Pulmonary lesions. B, bronchopneumonia (atypical pneumonia); R, right; L, left; u, upper; m, middle; l, lower. Effect on Course. The first of 2 numbers represents time from first dose of aureomycin to the first major persistent drop in fever, improvement in symptoms or definite evidence of clearing of the lungs, the second numbers indicate, respectively, the interval to the time when the patient became completely afebrile and symptom free and the lungs were clear by both physical and roentgen examination.

† This patient's treatment was started with daily intravenous injections of 500 mg (total 2 Gm.) all other doses were given by mouth.

‡ There was a sterile empyema in case 1 and probably some abscess formation in the lung in case 2. The course in these cases is shown in charts 1 and 2 respectively.

virus were also obtained in cases 8 and 12. In all, therefore, there was among these 13 patients definite evidence of influenza virus infection in 5 patients (4 with A and 1 with B organisms), titers strongly suggestive of similar recent infections in 4 others (3 with A and 1 with B organisms) and possibly in 2 additional cases (both with B organisms).

Results of Other Serologic Tests—Tests for cold agglutinins and for Streptococcus MG agglutinins were carried out in serums taken before treatment was started and at intervals thereafter in all but 1 (case 11) of these patients. Cold agglutinins could not be demonstrated in the lowest dilution tested (1:10 final) in any of the serums of 11 of these patients. In case 3, there was a titer of 1:40 in the serum obtained on the day before treatment was started, this was the fourth day of illness (the influenza and pneumonia were considered to have begun on the same day in this case), and the same titer was found in serums obtained through the next six weeks. The titer of Streptococcus MG agglutinins rose in this patient from 1:10 to 1:40 during this period. One other patient (case 4) showed an increase in titer of Streptococcus MG agglutinins from 1:20 to 1:80. The first blood in this patient was obtained on what was estimated to be the third day of the pneumonia and the ninth day after the onset of symptoms of influenza, and the rise was demonstrated one week later. No cold agglutinins could be demonstrated in any of the serums from this patient. In the remaining patients, the tests for Streptococcus MG agglutinins were either entirely negative (3 cases) or showed the same titers, ranging from 1:10 to 1:40, in all specimens taken during the acute and convalescent phases. The results of these tests, together with those for influenza antibodies, were interpreted as offering no support for the diagnosis of primary atypical (virus) pneumonia in any of these patients.

Condition of the Patients When Aureomycin Was Started—Treatment with aureomycin was begun during the first three days of the pneumonia in 8 cases, on the fourth or fifth day in 3 and on the sixth or seventh day in the remaining 2 cases. As already mentioned, none of these patients had previously received any antimicrobial therapy. All the patients were acutely ill and febrile when the first dose of aureomycin was given. The temperature at this time ranged between 101 and 105 F and was 103 F or higher in 10 of the 13 patients. The total leukocyte counts varied between 4,300 and 16,100, and in 9 of the patients these counts were below 12,000.

The pulmonary lesion as determined by physical examination and from the roentgenograms was limited to a single lobe in 10 cases and to two contiguous lobes of the right lung in 2 cases, it was bilateral in only 1 case. In most of the cases the lesions appeared in the roentgenograms as mottled or patchy areas of density with predominantly peri-

bronchial distribution or radiating out from the hilar region. In 4 cases, however, the physical and roentgenographic signs were those of lobar consolidation similar to those characteristically found in pneumococcal pneumonia. There were also musical rales heard bilaterally in most of the cases and showers of crepitant rales over the consolidated areas. Most of the patients had severe cough and complained of soreness over the sternum, but several complained of pleuritic pain and a loud friction rub was heard in 5 patients.

An attempt was made to estimate the severity of the illness in each case from the general appearance of the patients, the symptoms and other

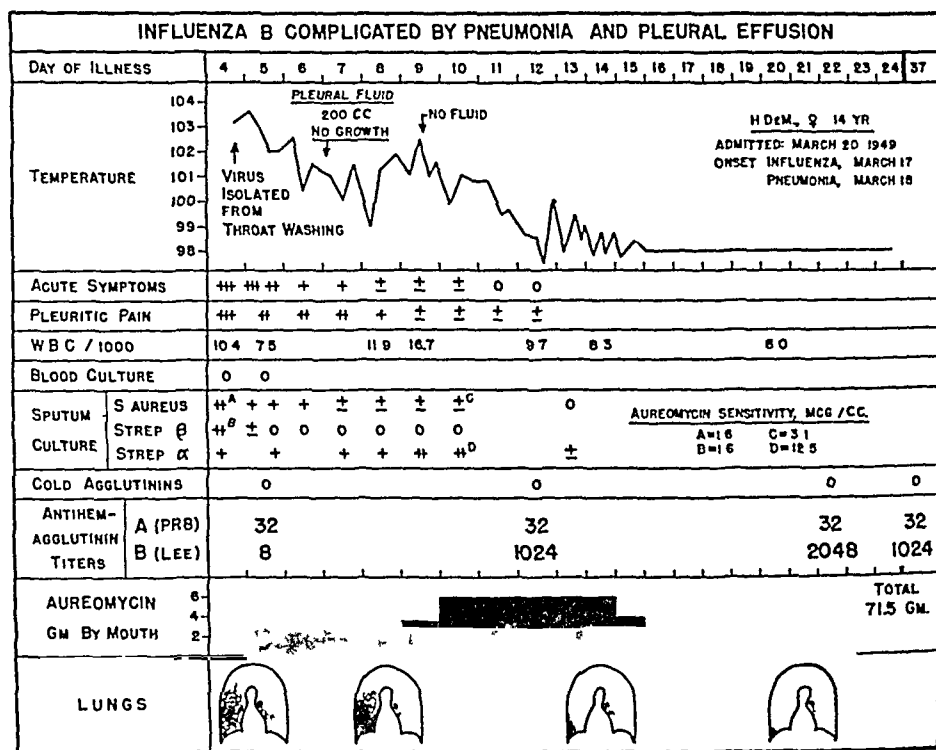


Chart 1—Course, treatment and relevant laboratory data in case 1

observations. The illness at the time aureomycin was started was considered to be severe in 5 cases, moderate in 7 and mild in 1.

Aureomycin Therapy—One of the patients who had a complicating pleural effusion received a total of 71.5 Gm. in eighteen days (case 1, chart 1). The total dose for the remaining 12 patients ranged between 6 and 24 Gm. and was given over a period of two to seven days. The average total dose of these 12 patients was 13.3 Gm. in an average of four and one-half days. One patient (case 7) received four daily doses of 500 mg. of aureomycin intravenously, and oral doses were used to continue the therapy in this case.

Effect of Aureomycin on the Course of the Disease—The course of the fever and symptoms after aureomycin was started was similar in the present cases to that observed in the aureomycin-treated cases of pneumococcic pneumonia¹ A major drop in the temperature occurred, except in case 1, in the first twelve to twenty-four hours, and only 2 patients had any fever after the second day of therapy In case 1 there was a sterile pleural effusion and the temperature dropped gradually during the first three days, but this was followed by a second bout of fever, lasting four more days In case 7 there was intermittent fever associated with pyrogenic reactions to intravenous injections during the second and fourth day

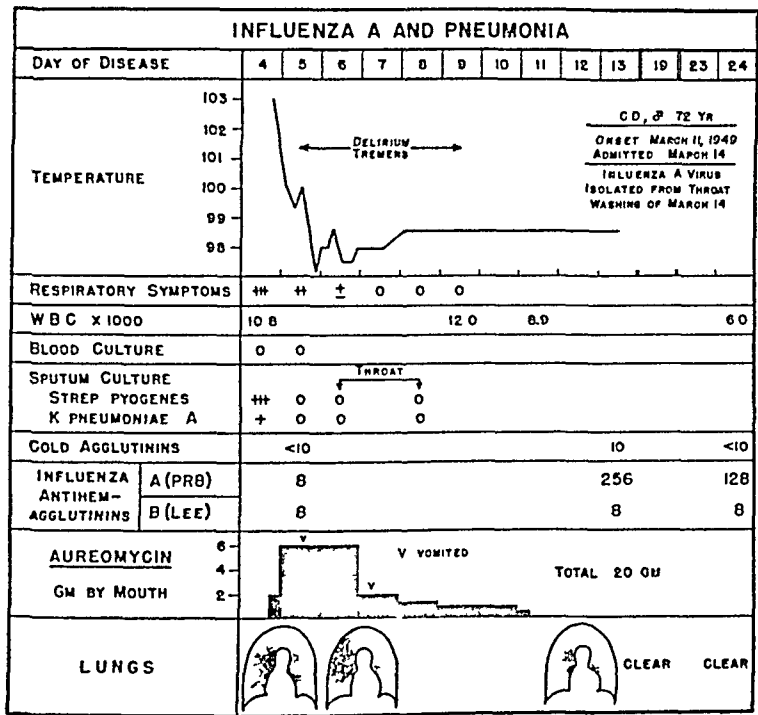


Chart 2—Relevant data in case 2

Symptomatically, all the patients were noticeably improved by the end of the first twenty-four hours, 10 were entirely free of symptoms by the end of the second day, and the remaining 3 continued to have pleuritic pain, raise blood-tinged sputum or had other minor complaints for three, six and seven days, respectively, after aureomycin was started

The lungs cleared rapidly, as judged by the physical and roentgen observations There was definite evidence of clearing of the lungs in all but 2 of the patients within the first four days The lungs were entirely clear roentgenographically by the end of a week after the first dose in 10 patients In case 1, in which there was a pleural effusion, in case 6, in which there was atelectasis of the middle lobe of the right lung, and in case 2 (chart 2), in which there was probably some abscess

formation in the upper lobe of the right lung, complete clearing of the pulmonary fields roentgenologically was delayed until fourteen to sixteen days after the use of aureomycin was started

Effect on Bacteriologic Findings in the Sputum—The predominant organisms found in the sputum were rapidly cleared after the start of aureomycin treatment, although the results in some cases were not so striking as they were in all cases of pneumococcic pneumonia¹. Cultures of sputum were made at frequent intervals during and after treatment in 9 of the cases. Hemolytic streptococci present in the sputum before treatment could no longer be demonstrated after the first day of aureomycin therapy in 4 cases and after the second, third and fourth day in 1 case each. In case 7, the hemolytic streptococci were still present in cultures of the sputum after seven days of therapy. There were 2 patients who continued to raise rusty sputum, 1 for 4 days and the other for six days after aureomycin was started, hemolytic streptococci could not be recovered from the sputum after the first day in the former and after three days in the latter.

Hemolytic *Staphylococcus aureus*, present in large numbers in the cultures made before treatment, could no longer be demonstrated after the first day of aureomycin therapy in 1 patient and after three or four days in 4 others. In case 1, these organisms were obtained in diminishing numbers during seven days of therapy but could not be obtained from subsequent sputum specimens. *K. pneumoniae* in case 2 could not be recovered from any specimens obtained after aureomycin was started.

Tests for sensitivity to aureomycin were carried out on most of the strains, and the results are indicated in table 1. It is of interest that the hemolytic streptococcus in case 7 was the least sensitive of the strains tested and required 12.5 micrograms for complete inhibition. *K. pneumoniae* was sensitive to 6 micrograms, and all other strains of hemolytic streptococci and staphylococci were completely inhibited by 3 micrograms or less. The sensitivity of all strains of the same organisms isolated from the same patient after aureomycin therapy was started was the same as before the start of treatment, and no evidence of increase in resistance could be found in any of the strains from this group of patients.

NONTUBERCULOUS PULMONARY SUPPURATION

The second group consists of 20 cases of the type in which the results of therapy at best are very difficult to evaluate. The patients ranged in age from 37 to 78 years, and only 5 were less than 50 years old. All but 3 of the patients were male. There was a history of underlying productive cough for varying periods in almost all these cases, and other serious underlying conditions played a significant or major role in most of them.

In almost all these cases the treatment with aureomycin was undertaken during an exacerbation of the chronic underlying bronchopulmonary infection, usually following some acute infection of the upper respiratory tract or pneumonia. The history of the underlying respiratory disease was usually long and complicated and many forms of therapy had been used. During the acute episode, except in case 24, treatment with other antimicrobial agents had been given for varying periods ranging from three days to several months before aureomycin was started. Aureomycin was given in these cases for varying periods while either some other agents were being continued or some other antimicrobial agents were given after it became apparent that no further benefit could be expected from the aureomycin.

In order to simplify the presentation, the data most relevant to the antimicrobial therapy and particularly to the evaluation of the effect of aureomycin in each case have been listed in table 2. Some of the pertinent aspects will be summarized briefly.

Condition of the Patients When Aureomycin Was Started—The severity of the disease in each of these patients was graded on the basis of the available clinical findings and from the general appearance at the time when aureomycin was started. Six of the patients were considered to be moderately ill, 10 were severely ill, and 4 were thought to be critically ill at the time. All but 5 of the patients were febrile, and most of them had slight to moderate leukocytosis.

The pulmonary lesion in most of the cases consisted of rather diffuse areas of patchy density in both lungs, particularly in the bases. There was also evidence clinically of chronic bronchitis and bronchiectasis in most of the cases. In a few cases there were large solitary or multiloculated abscess cavities in a single lobe with pneumonitis in the surrounding lung, and fluid levels within the cavities were visualized in the roentgenograms from time to time in such cases.

Bacteriologic Observations—All the blood cultures taken before administration of aureomycin was started showed no growth. A positive blood culture for type A K pneumoniae had been obtained previously in case 17, before that patient received streptomycin, but subsequent blood cultures in this case showed no growth.

The bacterial flora in the sputum of the patients varied considerably, but in most of them there were one or two organisms which were predominant in the pretreatment cultures. Coagulase-positive strains of hemolytic *Staph aureus* were the most frequent, these strains were all highly resistant to penicillin, the patients having previously been treated with massive doses of this antibiotic. Most of these strains of staphylococci were susceptible to aureomycin, being completely inhibited by 3 micrograms per cubic centimeter or less, but two of them

Case	Sex	Age	Predisposing Factors	Condition When Treatment with Aureomycin Was Started						
				Day of Disease	Previous Therapy		Predominant Organisms	Extent of Lung Involved	Temperature, °F	White Blood Cells
					Agent	Days				
14	F	51	Diabetic acidosis, pyelonephritis	10	Penicillin	3	Staph aureus ₂ , Str β ₃	B, bilateral	103	21,000
15	M	60	Hypernephroma, uremia	? 31 ? 3	Penicillin	3	Staph aureus ₂ , Ps aeruginosa ₁₀₀	B, bilateral	100	13,000
16	M	78	Bronchiectasis	32	Penicillin Sulfadiazine	26 21	Staph aureus ₂ , Ps aeruginosa ₁₀₀	B, Rlm, empyema	105	9,400
17	M	61	Chronic bronchitis	15	Penicillin Sulfadiazine Streptomycin	9 9 5	K pneumoniae A ₆ , Staph aureus ₂	L, Ru, abscesses	103	15,900
18	M	57	Bronchiectasis	20	Penicillin	10	H influenzae ₂	B bilateral	102	19,900
19	M	38	Hepatic cirrhosis, delirium tremens, diabetes	? 8	Penicillin Streptomycin	4 3	A aerogenes ₁₀₀ , Paracolon ₂₀₀	L, Rl	104	1,900
20	F	48	Chronic alcoholism, hepatic cirrhosis, jaundice	>57	Penicillin Sulfadiazine	46 28	Staph aureus ₂ , Str β ₂ , Enterococcus ₃	B, Lul, abscesses, empyema	102	30,000
21	M	66	Chronic alcoholism, diabetes, impetigo, paronychia	15	Penicillin Sulfadiazine	8 7	Staph aureus ₂	B, Ll, abscesses	102	21,000
22	M	55	Bronchiectasis, decubitus	31	Penicillin Sulfadiazine Streptomycin	30 24 4	Staph aureus ₃	B, bilateral, abscesses	101	15,800
23	M	56	Cerebral hemorrhage, hemiplegia, cardiac failure	15	Penicillin Sulfadiazine	18 15	Staph aureus ₂ , Str β ₁ , Ps aeruginosa ₁₀₀	B, bilateral, abscesses	103	3,100
24	M	58	Chronic bronchitis, bronchiectasis	3	None		Pneumococcus (type 20) ₂ , P vulgaris ₂₀₀	B, bilateral, atelectasis	103	16,000
25	M	57	Chronic alcoholism	56	Penicillin Sulfadiazine	4 23	A aerogenes ₂₀₀ , mixed flora	Abscess, Ru	99	6,200
26	M	46	Hemoptysis	6 mo	Penicillin Sulfonamides	25 23	Staph aureus ₆ , A aerogenes ₁₀₀	Abscess, Lu, ? brain abscess	98	6,100
27	M	49	Bronchiectasis, emphysema	28 yr	Penicillin	7	Staph aureus ₂ , P vulgaris ₂₀₀ , A aerogenes ₂₀₀	B, bilateral	98	12,000
28	M	52	Foreign body (tooth) inhaled	38	Penicillin Sulfadiazine	14 7	P vulgaris ₂₀₀ , A aerogenes ₂₀₀	Abscess, Lu	101	12,000
29	M	57	Bronchiectasis emphysema	Many years	Penicillin	30	H influenzae ₂ , A aerogenes ₁₂	Bilateral	98	12,900
30	M	65	Postpneumonectomy, empyema	24	Penicillin	15	A aerogenes ₂₀₀	Empyema	100	12,000
31	F	37	Pulmonary fibrosis, emphysema, asthma	12 mo	Penicillin Sulfadiazine	150 7	Staph aureus ₆ , P vulgaris ₁₀₀	B, bilateral	102	2,000
32	M	64	Hemoptysis	6 mo	Penicillin	22	Staph aureus ₃	Abscess, Lu B, Lul	100	12,000
33	M	61	Prostatic carcinoma, pyelonephritis, bronchiectasis	20	Penicillin Sulfonamides	18 13	Staph aureus ₂₀₀ , Ps aeruginosa ₂₀₀	B, bilateral	98	13,000

Explanations Day of disease refers to the particular episode under treatment in the chronic cases Other abbreviations are as in table 1

Estimated Severity	Aureomycin, Total Dose		Additional Therapy		Course and Complications Under Aureomycin	Estimated Benefit from Aureomycin
	Gm	Days	Agent	Days		
Critical	54	11	Penicillin	19	Steady defervescence and improvement in 9 days, <i>Ps aeruginosa</i> ₂₀₀ and <i>Monilia</i> replaced flora of sputum, <i>P vulgaris</i> ₂₀₀ persisted after <i>A aerogenes</i> ₂₀ cleared from urine (on catheter drainage)	Slight
Critical	415	8	Penicillin	8	Improved markedly first 2 days, then pulmonary edema developed, <i>Ps aeruginosa</i> ₂₀₀ replaced staphylococci, died eighth day	Slight, temporary
Severe	72	12			Afebrile in 3 days, improved markedly in 4 days, empyema cleared, lungs cleared 5 to 10 days, staphylococci rapidly cleared from sputum	Good
Severe	72	13	Penicillin	>13	<i>K pneumoniae</i> cleared from blood on streptomycin before aureomycin was begun but were found off and on in sputum and at operation and did not increase in resistance, large abscess drained surgically, gradually improved	Doubtful
Moderate	285	10	Penicillin	7	<i>H influenzae</i> replaced by <i>A aerogenes</i> ₂₅ then by <i>P vulgaris</i> ₂₀₀ , fever and symptoms improved steadily for 4 days, lungs cleared slowly (by roentgenograms) after 6 days	Good ?
Severe	0.81 m 73	1 17	Penicillin Streptomycin Sulfadiazine	18 2 >20	Type A <i>K pneumoniae</i> , cleared from sputum before aureomycin was started, fever persisted throughout therapy, but patient gradually improved after 4 weeks	Slight ?
Severe	30	12	Chloramphenicol	35	Staphylococci and streptococci promptly replaced by <i>P vulgaris</i> ₂₀₀ and <i>Monilia</i> , no effect from chloramphenicol, 120 Gm after aureomycin ended, partial resection and drainage with slow improvement	None ?
Severe	126	32	Penicillin Sulfadiazine	41 59	Marked and steady improvement after aureomycin was added to therapy, staphylococci cleared slowly in 17 days, replaced by <i>Ps aeruginosa</i> ₂₀₀ , afebrile after 6 days, lungs cleared almost completely	Moderate
Critical	65	12			Staphylococcal pneumonia followed <i>D pneumoniae</i> type 20 pneumonia with bacteremia that was cleared on previous therapy, markedly improved and afebrile in 3 days lungs cleared but marked fibrosis resulted in cardiac symptoms	Good ?
Critical	53	10	Sulfadiazine Chloramphenicol	4 9	Dramatic immediate improvement, <i>P vulgaris</i> ₂₀₀ rapidly replaced flora of sputum and stayed in urine (catheter drainage), chloramphenicol given when afebrile failed to clear proteus (sensitive to 20 µg/cc) from urine or sputum	Moderate
Severe	405	17	Chloramphenicol	4	<i>D pneumoniae</i> cleared rapidly but <i>P vulgaris</i> persisted in sputum, marked improvement in 36 hours, then gradual for 9 days, chloramphenicol later failed to clear <i>P vulgaris</i> from sputum	Moderate
Moderate	375	17			Amount and odor of sputum decreased rapidly (also had bronchoscopy and postural drainage), only <i>P vulgaris</i> ₂₀₀ and <i>A aerogenes</i> ₂₅ in sputum after aureomycin was started	Slight
Severe	21	7			Afebrile throughout staphylococci cleared rapidly, <i>A aerogenes</i> persisted and <i>P vulgaris</i> ₂₀₀ appeared, lung cleared partially, signs of ? cerebellar abscess on entry and persisted	Slight
Severe	54	19	Chloramphenicol	9	Sputum decreased in amount and became less purulent, <i>A aerogenes</i> and <i>P vulgaris</i> persisted and were not affected by chloramphenicol, remained afebrile	None ?
Moderate	825	14	Penicillin	8	Steady improvement, became afebrile, amount and odor of sputum reduced, also had bronchoscopy and postural drainage when aureomycin was started, almost cleared by roentgenograms	Moderate
Moderate	33	12			Sputum reduced in amount and became less purulent, <i>H influenzae</i> cleared promptly, improved generally and gained weight	Good
Severe	11 pl 100	22 23	Penicillin	26	Repeated intrapleural instillations of gradually increasing amounts 5-100 mg (buffered) of aureomycin, numbers of organisms dropped each time but then increased again, required repeated open drainage, sensitivity of <i>A aerogenes</i> in pleural fluid decreased from 25 to 100 µg	Slight, temporary
Severe	222 (Intermittent)	46	Streptomycin	30	Had 4 courses of aureomycin (longest 40 days), improved each time and relapsed when drug was stopped, died 12 months after first course	Slight, temporary
Moderate	115	31			Improved for 3 days after bronchoscopy and postural drainage, afebrile and more rapid improvement on aureomycin, <i>Staph aureus</i> persisted and sensitivity increased fourfold (was resistant to penicillin), lung healing, and sputum much decreased, <i>A aerogenes</i> ₁₀₀ and <i>Ps aeruginosa</i> ₂₀₀ appeared during second week and persisted	Moderate
Moderate	43	15			Continued to cough and raise purulent sputum, staphylococci cleared slowly and <i>Ps aeruginosa</i> later found in pure culture in sputum and urine	Doubtful

required 6 micrograms and one required 25 micrograms for complete inhibition. Hemolytic streptococci in large numbers were isolated from 3 patients and *Hemophilus influenzae* from 2 others, all these strains were sensitive to 3 micrograms per cubic centimeters or less.

There were 2 cases of type A *K. pneumoniae pneumonia* in this group. In both of them (cases 17 and 19) streptomycin and penicillin had been used before the aureomycin was started, in 1 of them the organisms were no longer demonstrable in the blood, and in the other they could not be obtained from cultures of the sputum after aureomycin was started. In each of the 2 cases there was extensive abscess formation which appeared to be progressing, and both patients were still acutely ill when aureomycin therapy was started. The strains of *K. pneumoniae* from both of these patients were highly sensitive to streptomycin before that antibiotic was given, and the strain isolated before aureomycin treatment in case 17 was just as sensitive to streptomycin as the original strain in that case.

In the remaining cases the predominant organisms were mainly of the type more frequently encountered in chronic infections of the urinary tract, namely, *Aerobacter aerogenes*, *Proteus vulgaris* and *Pseudomonas aeruginosa*. Most strains of these organisms were moderately to markedly resistant to aureomycin, requiring 25 to 200 micrograms per cubic centimeter for complete inhibition.

In case 24, *Diplococcus pneumoniae* type 20 was found in the initial sputum specimen and was identified in smears and cultures. The pre-treatment sputum specimen, however, showed a predominance of gram-negative bacilli, and *P. vulgaris* also predominated in the surface cultures of this sputum.

Dosage—Larger doses were used and were given over longer periods in these cases than in those of group I. The total oral dose varied from 21 to 222 Gm given over periods ranging from seven to forty-six days. The patient who received the largest amount (case 31) was given aureomycin intermittently for one to three weeks at a time over a period of several months. In all the other cases the entire dose was given more or less continuously. The intravenous route was used exclusively in case 15, 500 mg being given daily for eight days. The average oral dose in the remaining 19 patients was 70 Gm given over an average of seventeen days.

Effect of Aureomycin on the Clinical Course—The effect on the clinical course is summarized in table 2 for each of the patients. Most of them showed some improvement in their general condition soon after the aureomycin was started, and in some of those who were severely or critically ill at the time the immediate improvement was dramatic. The temperature usually declined slowly. The sputum, in those in whom it was foul, lost its odor in most cases. The amount of sputum

raised was usually decreased markedly, and some of the patients stopped raising any sputum. The character of the sputum in other cases changed from purulent to mucoid.

Improvement in the pulmonary lesion as judged from the physical signs and the roentgenograms also varied considerably. There was marked and fairly rapid clearing in some of the cases, but in most instances this occurred slowly. Surgical drainage of abscesses was required in only 2 of the cases, including 1 case of *K. pneumoniae* infection (case 17).

Just how much of the improvement that was observed could be ascribed to the aureomycin was sometimes difficult to assess. In an occasional case drainage improved after bronchoscopy, and in other cases postural drainage was being carried out with good effects during the time that aureomycin was being given. Since similar procedures were also done in these and other cases during the antecedent therapy, which included systemic and aerosol administration of penicillin in many cases, it was felt that the aureomycin was responsible, in large measure for the observed improvement. A rough evaluation of the benefit derived from the aureomycin in each case is shown in the last column of table 2.

Two of the patients died. In 1 case (case 15) death resulted from hypernephroma and uremia, the latter already rather severe when the aureomycin was started. In this case there was marked improvement during the first two days of intravenous aureomycin therapy. In the other case (case 31) death occurred almost a year after the patient received the first course of aureomycin. This patient was almost moribund when the aureomycin was first given, and she was noticeably improved for several weeks at a time during and after each course of aureomycin.

Effect on the Bacteriologic Flora of the Sputum—The effects of aureomycin treatment on the bacteriologic flora of the sputum in these cases were similar to those noted in the urine in cases in which treatment was given for infections of the urinary tract⁶. The susceptible strains were cleared rapidly in most cases and somewhat more slowly in others. In the majority of the cases relatively resistant organisms, usually *P. vulgaris*, *A. aerogenes* or *P. aeruginosa*, replaced the strains of sensitive organisms. Increase in resistance of strains of the same organisms isolated during or after the course of aureomycin was noted only in case 30. In this case aureomycin was given orally and was also instilled intrapleurally in increasing amounts over several weeks. After each intrapleural instillation the number of organisms in the exudate decreased markedly, as did the amount of exudate, but these changes were only temporary. In this case the strain of *A. aerogenes* when originally

6 Collins, H. S., and Finland, M. Aureomycin Treatment of Urinary Tract Infections, Surg., Gynec. & Obst. 89: 43-48 (July) 1949.

isolated was sensitive to 25 micrograms of aureomycin per cubic centimeter, and the organisms obtained after several weeks required 100 micrograms for complete inhibition. In all other cases, all strains of the same organisms isolated before, during and after aureomycin therapy had the same sensitivity to this antibiotic.

Effect of Additional Antimicrobial Therapy—In two thirds of the cases further therapy with sulfonamides or other antibiotics, singly or in combination, was given after the course of aureomycin was concluded or during the latter part of the aureomycin treatment. There was little if any additional beneficial effect observed from these agents either on the clinical course or on the bacteriologic findings. Of particular interest are the cases of 4 patients (cases 20, 23, 24 and 27) to whom chloramphenicol (chloromycetin®) was given in doses of 4 to 6 Gm a day in attempts to clear the sputum of organisms, particularly *P. vulgaris*, that persisted during the aureomycin therapy. In none of these 4 cases was any additional beneficial effect on the clinical course, on the pulmonary lesion or on the bacteriologic findings observed during the administration of chloramphenicol.

TOXICITY

The untoward effects from aureomycin in the present cases were of the same character and frequency as those observed in other groups of cases that have been studied here. They were limited almost entirely to gastrointestinal symptoms. Vomiting or nausea occurred during oral therapy in 9 of the cases of group I and in 11 of those in group II. Loose and frequent bowel movements were experienced in a total of 5 cases in both groups, including those of 4 patients who also had gastric symptoms. There were also 2 cases in group II in which the patients complained of slight dizziness after more than a week of therapy. In a third case (case 32) of this group the tongue appeared red and smooth at the end of a thirty-one day course. The last 3 patients also vomited several times during the latter part of their therapy. There were 4 cases in group I and 7 in group II in which the patients experienced no untoward effects whatever.

It is of interest that among the patients who experienced nausea and vomiting from the aureomycin this was transient in some, occurred only after two or more days of therapy in others and in several was experienced only on the largest oral doses (1 Gm every four hours) and did not occur after the dose was reduced to 0.5 Gm every four hours. Among those who had some untoward gastrointestinal symptoms were 9 patients who received more than one lot of aureomycin, each preparation being given for three to seven or more days in doses of 1 Gm every four or six hours. Five of these patients had these symptoms from only one of two lots and not from the other, 1 patient had them from

one of three and another from one of four lots and not from the other two and three, respectively. One additional patient received four lots, and another received six different lots, the former had untoward effects from two and the other from four of these lots.

The patient who received part of the aureomycin intravenously (case 7) experienced mild pyrogenic reactions from the second and the fifth dose, but there were no reactions in case 15 in which all of the aureomycin was given intravenously. One patient who received eight intramuscular injections of 100 mg each during the first day had considerable local pain and tenderness. In case 30 there were no untoward reactions when small amounts of aureomycin were injected intrapleurally, but when 50 or 100 mg was instilled the patient complained of a "hot sensation" in the chest that lasted several minutes.

In no instance was there any fever or rash that could be attributed to the aureomycin. There were no detectable untoward effects on the blood, kidneys, liver and nervous system in any of the patients.

COMMENT

The results of aureomycin therapy in these two groups of cases indicate clearly both the versatility and the limitations of this antibiotic in the treatment of nontuberculous bacterial infections of the lungs. In the acute cases of group I in which only sensitive bacterial strains appeared to be involved, the clinical results were uniformly good. Furthermore, the rapid disappearance of the susceptible organisms, although not quite so striking in these cases as they were in the cases of pneumococcal pneumonia, was nevertheless impressive. This served to confirm the impression that the observed benefits were indeed ascribable to the action of the aureomycin.

The only significant complication encountered in this group was a sterile effusion in case 1. This most probably represented a metapneumonic empyema which had been rendered sterile by therapy. The fluid obtained was purulent, contained 59,000 leukocytes per cubic millimeter, almost all of them polymorphonuclears, and showed no organisms on direct smear and no growth on culture. Two days later, an attempted thoracentesis in this patient yielded no fluid. There was also atelectatic collapse of most of the middle lobe of the right lung in 1 other patient, and this was only temporary. In case 2 these may have been early abscess formation which healed rapidly and completely.

In most of the cases of group II, extensive tissue damage was already present as the result either of some underlying bronchopulmonary disease or of the immediate acute infection that was not entirely arrested by antecedent therapy. The amount of benefit derived from the aureomycin in the individual cases appeared to depend largely on the nature of the offending organisms, their susceptibility to aureomycin and the

extent and character of the pulmonary lesions. In cases in which relatively resistant organisms were present from the start or appeared in predominant numbers, in which there were extensive suppurative lesions that were not draining adequately or in which there were more serious underlying lesions, the effects from aureomycin were slight or equivocal.

The findings in these cases do indicate, however, that some benefit may be expected from aureomycin in a considerable proportion of cases of nontuberculous bronchopulmonary suppuration after other antimicrobial agents, particularly sulfonamides, penicillin and streptomycin, either have failed completely or have given only partial or slight relief. The failure of organisms to develop resistance to aureomycin during the course of treatment, which is similar to penicillin in this respect, is an important feature of the treatment of protracted infections. The presence of other unhealed lesions or the improper drainage or absorption of suppurative foci, however, predispose to additional infections with insensitive organisms during treatment with aureomycin, just as they do during penicillin therapy.

Although chloramphenicol failed to bring about any additional improvement in the 4 cases of this group in which it was used after the aureomycin, no conclusions are justified concerning its effectiveness in similar cases if it were used in the same manner that aureomycin was used here or if it were used to initiate therapy in similar cases.

SUMMARY AND CONCLUSIONS

Aureomycin alone was highly effective in the treatment of a group of 13 cases of acute bacterial, nonpneumococcic pneumonias. Most of these cases probably occurred as complications of influenza viral infections.

The effects of aureomycin therapy in 20 cases of nontuberculous bacterial bronchopulmonary infection were variable. The best effects were observed in cases in which aureomycin-susceptible organisms were primarily concerned. The beneficial effects were limited, however, because of the replacement of some of these susceptible organisms by relatively resistant ones. In almost all these 20 cases the aureomycin was started after other antibacterial agents had been given without effect or with only limited benefit. Subsequent use of similar antibacterial agents in most of these cases, including chloramphenicol in 4, failed to produce any further appreciable beneficial effects.

STERNAL MARROW IN PATIENTS WITH METASTATIC CANCER

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SOME TIME ago the chance diagnosis of metastatic carcinoma first made by means of sternal aspiration stimulated my interest in the procedure and led to a search for further information. It seemed probable that metastatic tumor cells could be found in bone marrow more frequently than has been supposed if only the proper search were made. A study of bone marrow smears obtained by sternal aspiration from 32 patients with known or suspected metastatic carcinoma or sarcoma has been carried out in an effort to determine the pattern of reaction of the marrow to cancer. The findings of this study together with a brief review of the available literature are reported.

REVIEW OF THE LITERATURE

Literature in the English language concerning hematologic and cytologic observations in patients with cancer is sparse. Standard texts make only brief mention that occasionally tumor cells may be found on sternal aspiration¹. I have been able to find few detailed studies of the cytology of tumor cells as shown on smears and imprints stained with Wright's and Giemsa stains.

Paul Ehrlich and Lazarus,² in their monograph on the histology of blood published in 1900, discussed the changes in the blood arising from tumors by citing 2 cases reported by Nathnagel and by Israel and Leyden. In the first case the peripheral blood showed "simple severe anemia" with isolated normoblasts, small marrow cells and a moderate leukocytosis. No mention was made of tumor cells in blood. At autopsy the skeletal system showed complete atrophy of bone marrow and replacement by tumor cells. As sternal aspiration did not become preva-

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1 Wintrobe, M. M. *Clinical Hematology*, ed 2, Philadelphia, Lea & Febiger, 1946. Piney, A., and Hamilton-Paterson, J. L. *Sternal Puncture*, ed 3, New York, Grune & Stratton, Inc., 1946.

2 Ehrlich, P., and Lazarus, A. *Histology of the Blood Normal and Pathological*, edited and translated by W. Myers, University Press, Cambridge, 1900.

lent until after 1930, the tumor cells which might have been discovered by study of the sternal marrow were not found ante mortem. In the second case there was the usual degree of anemia without an unusual leukocyte picture. Ehrlich cited a third case of Epstein's, in which there were considerable anemia, numerous nucleated red blood cells "both of the normo- and megaloblastic types," leukocytosis and increase in large mononuclear forms (description not given) without significant eosinophilia. Autopsy proved metastatic carcinoma of bone marrow. No additional observations of their own experience were recorded by Ehrlich and Lazarus.

Nordensen's³ monograph published in 1935 contains a report of a study of sternal marrow from more than 160 patients, including some hematologically normal persons, some with primary blood dyscrasias and some with various other types of disease. Among the last-mentioned group were 17 patients with various types of cancer. In none of them did Nordensen directly describe tumor cells. In 2 instances he described "large granular cells with loose nucleus and peculiar shape and plentiful cytoplasm which is sometimes vacuolated and slightly basophilic with hypergranulation." These cells were not classified more specifically. In 10 of the 17 cases there was a shift to the left in the myeloid series, in the majority of cases the marrow was said to be "cellular", in only 4 cases did he report numerous reticuloendothelial cells, and in 11 cases he stated that eosinophilic cells were "scarce," "rare" or "strikingly few." He cited Plenge as saying that both cancer and sepsis have an inhibitory effect on granulopoiesis and that there is no essential difference in marrow in patients with cancer with and without infection.

Rohr and Hegglin⁴ studied and reported on the sternal marrow of 74 patients with malignant tumors, 10 had malignant cells in the smears. They described malignant cells as characterized by anisocytosis, an extraordinarily large nucleus with a large nucleolus and an increased ratio of nucleolus to nucleus. These authors asserted that a diagnosis may be made from a single cell in the smear if it is from a large cell type of tumor but that groups are necessary if the cells are from the small cell type tumor. They tested some of their cytologic characteristics by making direct smears from primary and metastatic nodules and staining with Wright's and Giemsa stains, as if the smears were from bone marrow. They expressed the belief that the appearance of the cells so obtained is identical with that of the tumor cells found on aspiration. Five of the patients with smears positive for cancer had bronchogenic

3 Nordensen, N. G. *Studies on Bone Marrow from Sternal Puncture*, Stockholm, Bortzells, Esselte, 1935.

4 Rohr, K., and Hegglin, R. *Tumorzellen im Sternalpunktat*, *Deutsches Arch f klin Med* **179** 61, 1936.

carcinoma, 2, gastric carcinoma, 1, prostatic carcinoma, and 2, retroperitoneal sarcoma

Kreyburg and Poppe⁵ aspirated marrow from 100 patients and made parallel series of smears and of sections of fixed and embedded preparations. They found tumor cells in preparations from 8 of the 100, and all 8 were patients who showed clinical and roentgenologic evidence of metastases. These authors did not describe the characteristics of the cells in detail but, rather, utilized histologic criteria of the tissue obtained in diagnosing the presence of malignant cells. From their study they concluded that the fixed and sectioned preparations are more useful in making such diagnoses. Three of the 8 patients with sections positive for tumor cells had carcinoma of the breast, 3 had carcinoma of the prostate gland, 1 had carcinoma of the stomach and 1 had multiple myeloma.

Schleicher,⁶ too, utilized both the imprint and the histologic technic to point out the value of sternal aspiration in finding tumor cells. He also stated that fixation and sectioning give a greater number of positive diagnoses.

METHOD

As it was the purpose of this investigation to discover how often on routine examination by technics already widely used one may find tumor cells in the bone marrow, no special technics were used for the principal portion of the study.

The sternum was selected for aspiration, as it is my preferred site. The needle was inserted into the marrow cavity at the level of the second interspace. Approximately 0.25 to 0.5 cc of marrow was aspirated and immediately flooded onto clean slides. In this way marrow "units" might be seen readily as light yellow-white flecks floating in the blood when the slide was held against the light. These units were picked out singly with applicator sticks and transferred to cover slips to make the conventional cover slip smears. Smears were stained with Wright's stain and counterstained with Giemsa stain.

From 10 to 20 preparations from each patient were scanned under low power and then under high power with dry and oil immersion objectives. General impressions were gained as to activity, types of cells predominating and presence or absence of tumor cells. At least 250 to 300 cells were counted for a differential count, but it was recognized that such differential counts are only approximations and ought not be considered absolute in any respect.

Cytologic criteria for malignancy were considered to be as follows:

- 1 The general structure and staining qualities of the cells are at variance with those of normal cells in normal bone marrow.
- 2 The cells are usually large, 15 to 25 microns.

5 Kreyburg, L., and Poppe, E. Tumour Cells in Sternal Bone-Marrow, *Lancet* 1:593, 1940.

6 Schleicher, E. M., and Fahr, G. The Value of the Sternal Portion of the Bone Marrow in Diagnosis, *Minnesota Med* 28:669, 1945.

3 Cytoplasm is abundant or scanty, basophilic, frequently vacuolated and rather foamy, especially in adenocarcinoma

4 Cells possess hyperchromatic nuclei which vary in size

5 Nucleoli (numbering 1 to 3) are prominent

6 Numerous mitotic figures may sometimes be seen

7 The cells usually occur in groups, nests or sheets, but many occur singly or in small groups, only two or three together, when the cells do occur in nests or sheets, of course, there is no question as to their identity, but when they appear in small numbers only, definite identification is more uncertain

8 Metastatic cells appear undifferentiated and often resemble undifferentiated stem cells of the reticuloendothelial system

To check this list of criteria as opportunity arose at autopsies or surgical biopsies, direct smears from cut surfaces of tumor nodules were made and stained by the technic described. The cytologic details agreed closely with those observed

TABLE 1—*Distribution of Cases According to Type of Primary Cancer*

Carcinoma of breast	5
Carcinoma of stomach	4
Carcinoma of prostate	3
Carcinoma of bronchus	2
Multiple myeloma	2
Carcinoma of cervix	2
Osteogenic sarcoma	2
Carcinoma of large bowel	2
Carcinoma of kidney	2
Carcinoma of pancreas	1
Reticulum cell sarcoma	1
Primary site undiagnosed	6
Total	32

on the smears of bone marrow. From the experience gained in this work it may be said that the cytologic qualities as set forth here are the qualities of malignant cells in general when those cells are stained by a Romanowski technic.

SELECTION OF CASES

In this study patients who were known to have or were strongly suspected of having metastatic lesions were selected. No regard was given to the source of the primary tumor. Those which frequently metastasize to bone were not selectively chosen. An effort was made to collect as large a series as possible. In table 1 is shown the distribution of the 32 cases as to primary site. The patients were 12 women and 20 men. Two were in the third decade of life, 11 in the fifth, 8 in the sixth, 10 in the seventh and 1 in the eighth. A brief summary of the clinical history of each patient is appended to this article.

OBSERVATIONS

The appearance of the bone marrow of these patients varied considerably, but in most instances the marrow did not present a strictly normal distribution of one or more of the cell types, even when tumor cells were not found. In table 2 the distribution of cells and the findings in

the cases are summarized Wintrobe figures are taken as the normal In 8 of the 32 cases, cells possessing the criteria for malignancy, as set forth in a previous section, appeared in small groups, clumps or sheets permitting the unequivocal diagnosis of metastatic tumor In 4

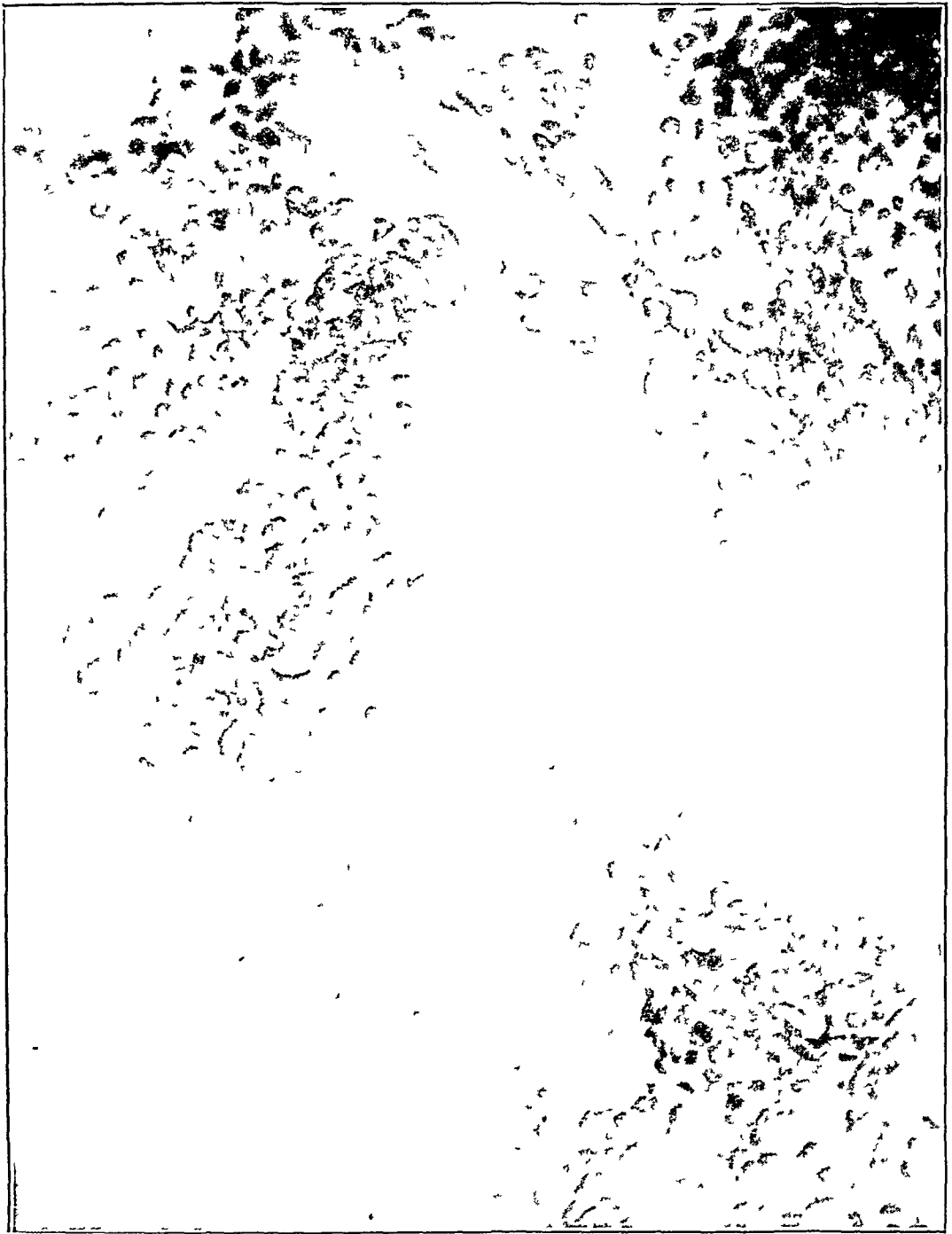


Fig 1 (case 2)—Aspirated marrow, showing complete replacement of normal marrow with tumor tissue, $\times 220$

more cases scattered throughout various smears were single cells with similar appearance, suggesting the presence of metastatic tumor I am unwilling, at present, to make an unequivocal diagnosis of cancer

TABLE 2—Summary of Ca

Case No	Diagnosis	Hema tocrit, %	Red Blood Cells, Mill	Hgb Gm	White Blood Cells, Thous	Type of Marrow	Eos Myel	Eos	Bas Myel	Bas	Myelobl	Pro myelo	Myel	Meta
1	Ca lung†	34	39	11.3	50	Cellular	65	00	00	05	00	15	20	20
2	Ca stomach		38	10.9	26	No normal marrow								
3	Ca breast					Too little normal marrow								
4a	Ca lung		44	14.0	13.0	Cellular	28	20	00	00	04	04	56	17.2
4b	Ca lung					Cellular	43	07	00	00	03	06	67	13.3
5	Ca bronchus		20	5.5		Poorly cellular	70	25	10	00	00	15	100	12.5
6	Multiple myeloma	45		14.4	10.2	Very cellular								
7	Ca cervix		44	14.7	5.0	Cellular	20	08	00	00	04	08	104	18.8
8	Retroperitoneal sarcoma	31	39	11.5	10.8	Very cellular	55	35	00	00	10	40	120	12.0
9	Multiple myeloma or metastatic Ca		39	12.0	6.3	Poorly cellular	00	25	00	00	00	00	15	7.0
10	Ca stomach					Cellular	45	25	00	00	00	35	11.5	17.0
11	Ca prostate	34				Cellular	46	40	00	00	03	20	130	9.7
12	Osteogenic sarcoma	44		15.7		Cellular	32	04	08	00	08	20	80	16.8
13	Ca breast					Cellular	15	05	00	00	10	20	130	13.5
14	Ca primary (?)		27	7.4	9.6	Moderately cellular	32	04	08	04	04	24	156	20.0
15a	Ca breast	32	33	11.0	6.1	Very cellular	66	22	00	00	02	06	86	9.4
15b§	Ca breast		3.5	11.0	11.2	Very cellular	56	13	00	00	03	09	56	10.0
16	Ca colon					Very cellular	76	16	00	00	08	12	84	12.0
17	Ca pancreas			16.9	16.0	Cellular	00	15	05	00	05	05	165	9.0
18	Ca primary (?)		29	7.6	14.1	Cellular	20	08	00	00	04	12	164	18.4
19	Ca prostate					Moderately cellular	32	36	00	00	16	56	188	12.8
20	Ca cecum	15	23	8.5		Very cellular	40	15	00	00	05	05	90	5.0
21	Adenoca primary (?)	41		14.8	11.5	Moderately cellular	44	20	04	00	04	36	96	10.8
22	Adenoca kidney	30	43	9.4	14.5	Cellular	40	24	00	00	04	33	100	14.4
23	Ca breast	37	43	12.5	9.4	Cellular	50	35	00	00	05	25	355	12.0
24	Myeloma	35	38	11.8		Cellular	20	10	05	05	10	15	75	13.5
25	Osteogenic sarcoma	31	33	9.8		Very cellular	16	16	04	04	00	00	240	14.4
26	Ca stomach	26	36	8.0		Moderately cellular	12	16	00	00	08	20	72	13.6
27	Ca prostate		38	12.5	5.4	Very cellular	55	10	20	00	05	25	210	14.0
28	Ca primary (?)	20	19	6.2	Leukocytosis	Cellular	12	00	04	04	04	20	52	22.4
29	Ca cervix		29	9.5	6.7	Cellular	35	15	00	00	00	05	50	23.5
30	Ca stomach	34	34	11.3	8.4	Moderately cellular	40	12	00	00	08	20	80	21.2
31	Ca kidney	41	5.5	15.0	4.2	Very cellular	00	1.6	00	00	00	2.4	18.0	13.6
32	Ca breast		27	8.0	7.0	Cellular	08	04	00	00	04	24	2.4	26.4

* These cells were deeply basophilic, with abundant foamy cytoplasm and prominent nucleoli

† These cells were characterized by dense chromatin, vacuolated cytoplasm and prominent nucleoli

‡ These cells had deeply basophilic cytoplasm, a loosely clumped nucleus and large nucleoli

§ Same case as 15a two months later.

Tab forms	Seg	Lymph	Mono	R-E	Plasma	Pro eryth	Erythd	Normoblast		Mega	M F	Abnormal Cells	Metas- tases (X Ray)
								Early	Late				
155	580	75	40	30	55	00	00	10	05	+		Several clumps of tumor cells, many plasma cells atypical	+
							.	Absent				Sheets of tumor cells*	+
								Absent				Similar to case 2	+
228	136	92	08	28	56	00	08	32	124	+	04	None	0
293	77	37	03	13	43	00	17	40	207	07	03	None	0
290	125	55	15	30	20	00	05	30	75	05	05	None	0
					30-40%							Abnormal plasma cells in clumps, many with 2 nucleoli	0
224	48	88	04	28	36	00	08	52	180	+		One group of 4 cells together †	0
35	30	50	00	10	15	05	05	25	175	05	25	None	0
80	320	130	00	10	120	00	05	10	180	+		Many abnormal plasma cells, groups of larger cells ‡	+
220	90	50	00	30	105	00	00	05	65	15		Fields 10-12 plasma cells, 3% unclassified	+
143	37	97	00	13	27	00	10	63	253	07	13	None	+
216	92	52	04	12	36	08	08	72	160	16	04	None	0
80	25	140	00	20	25	10	10	65	295	+	15	Increase in plasma cells, many in groups of 5-8, no tumor cells	+
304	64	56	00	08	16	00	00	28	92	+	?	Occasional atypical cells	0
222	54	68	00	26	30	02	12	32	164	06	08	No tumor cells, megakaryocytes very plentiful	+
56	83	33	00	23	26	03	13	73	216	13	10	Nests of tumor cells (2) on 4 smears, megakaryocytes greatly increased	+
220	36	120	08	16	16	00	12	40	304	04	08	None	0
290	135	85	00	10	30	10	25	65	150	10	00	Scattered atypical cells, many megakaryocytes	+
232	68	20	00	12	88	04	12	32	136	+	04	None	+
130	48	40	04	28	48	00	04	20	17	+		None	+
100	25	30	00	35	45	10	30	75	375	05	15	Plasma cells in groups 4 to 6	0
158	84	120	04	36	08	04	08	44	180	04	08	None	+
300	40	24	00	08	32	00	04	28	212	+	12	Occasional atypical cell	+
220	30	80	05	15	60	00	00	15	80	+	05	None	+
160	80	130	00	15	75	15	10	50	215	+	00	Abnormal plasma cells, few with 2 to 3 nuclei	+
160	40	52	00	16	72	00	04	60	164	04	00	None	+
230	108	60	12	28	16	00	12	32	172	12	00	04% unclassified, stem cells?	0
290	100	20	20	10	35	00	00	50	200	Many	05	None	+
452	52	40	16	36	28	00	16	120	308	+	12	Groups of 3, 4, and 6 on 3 different slides, scattered single cells	0
545	140	35	00	20	05	00	00	20	80	10	05	None	0
268	64	100	00	12	04	04	04	40	128	+	04	None	0
640	64	60	04	72	124	00	00	08	68	04	16	84% unclassified, probably tumor cells, many plasma cells abnormal	?
196	24	28	00	08	08	00	28	84	384	04	04	None	

on the presence of single cells only, although I feel certain that such a declaration can probably be made as one gains more and more experience

There were other unusual features brought out by these studies that seem at variance with what previous workers have reported Nor-



Fig 2 (case 6) —Bone marrow showing a large percentage of abnormal plasma cells or myeloma cells, $\times 470$

densen distinctly pointed out that in the majority of his 17 patients with cancer eosinophilic cells were infrequent Contrariwise, it is shown here that in nearly half (44 per cent) of the patients a distinct increase in eosinophilic elements appeared and the remainder showed a number

at least within normal limits. Most writers mention only briefly or make no point at all of the number and appearance of the reticuloendothelial cells and plasma cells. In this series one of the most striking and consistent findings was an increase in the number of plasma cells and reticuloendothelial cells. Twenty-one patients had an elevated number

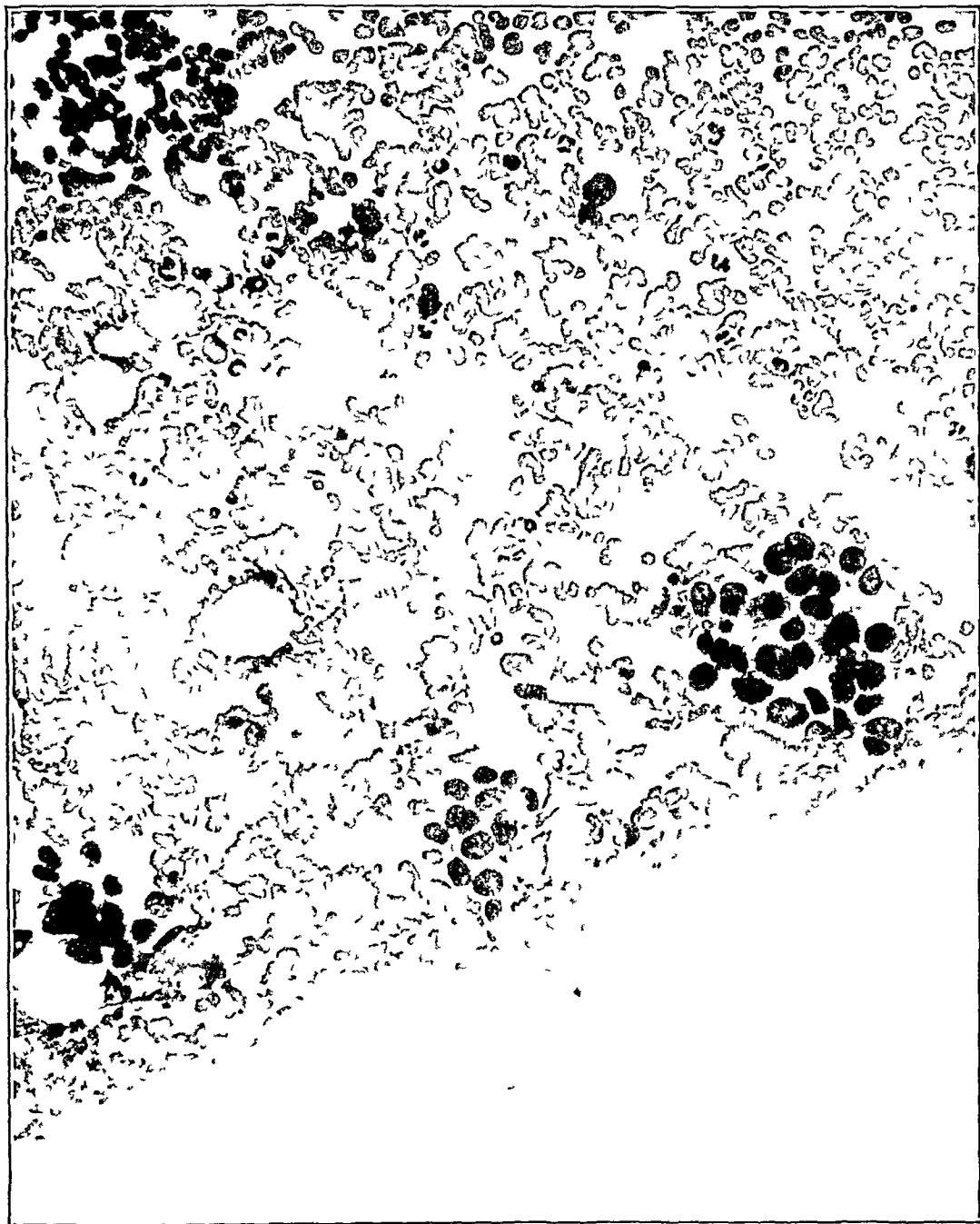


Fig 3 (case 3)—Bone marrow showing several nests of tumor cells. Note also single tumor cells scattered through smear, $\times 220$.

of plasma cells, and 12, an increase in reticuloendothelial cells. Not only the number but also the character of these cells was abnormal. In several of these cases the plasma cells occurred in large clumps, of 10 to 15, the typical "wheel spoke" clumping of the chromatin had

disappeared, the cytoplasm was foamier and often contained azurophilic granules. In 2 instances, cases 10 and 31, if one did not have clinical or autopsy information, a diagnosis of multiple myeloma would have been seriously entertained from the cytologic study alone. In case 31, the patient had a plasma globulin content of 5 Gm and a uric acid content of 10 mg to help support the case for myeloma, but, as noted in the protocol, autopsy revealed a massive renal carcinoma with widespread metastases. M S (case 10) had a large adenocarcinoma of the stomach with metastases to nearly every conceivable location.

TABLE 3—*Summary of Chief Observations*

	Cases	
	Number	Percentage
Cases studied	32	100
Definitely positive bone marrow	8	25
Doubtfully positive bone marrow	4	12.5
Anemia	22	68.75
(Female Hematocrit <35%, or <3,900,000 red blood cells or <110 Gm Hgb)		
(Male Hematocrit <40%, or <4,200,000 red blood cells or <125 Gm Hgb)		
Leukocyte count above 10,000	8	25
Leukocyte count below 5,000	2	6.25
Leukocyte count 5,000 to 7,500	7	21.9
Leukocyte count 7,500 to 10,000	3	9.4
Plasma cells in bone marrow increased 25 per cent or more	22	68.75
Reticuloendothelial cells in bone marrow increased 25 per cent or more	12	37.5
Reticuloendothelial cells and plasma cells both increased	8	25
Eosinophilic cells increased	15	46.9
(Myelocytes 4 per cent or more, older cells 4 per cent or more, combined 7 per cent)		
Cellular to very cellular bone marrow	25	78.1
Poorly cellular bone marrow	2	6.25
Erythroid elements decreased 8 per cent or less	5	15.75
Megakaryocytes notably increased	4	12.5
One or more abnormalities of the bone marrow	23	87.5

Almost all the patients showed a very cellular marrow, in only 2 was it poorly cellular, and in only 3 were the erythroid elements depressed below the lower limits of normal despite the fact that over half the patients had anemia. In a few patients, Mrs F H (case 15) being an outstanding example, the number of megakaryocytes in the bone marrow was notably increased.

Table 3 presents a summary of the significant findings in the series.

COMMENT

It would appear from the cited observations that it is possible in a fair percentage of cases actually to observe malignant cells in sternal marrow obtained by routine aspiration and stained with ordinary blood stains.

Clinically the finding of tumor cells testifies to the lateness of the process. It is not inconceivable, however, that the sternal marrow may actually be the first clue to the nature of the disease process going on in the patient, and it therefore behooves the examiner to search diligently

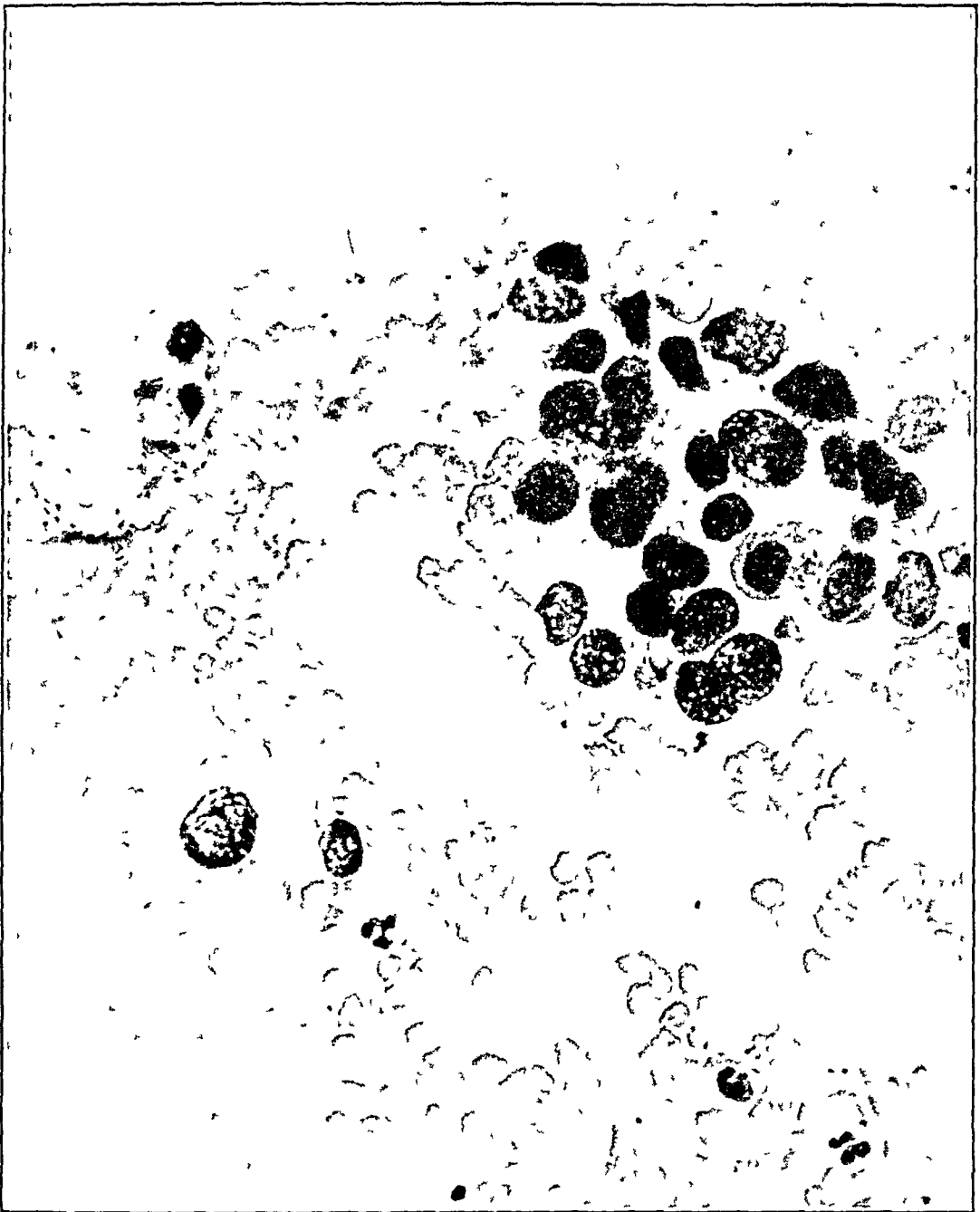


Fig 4 (case 3) —High power magnification of one of clumps seen in figure 3. Note variation in size and shape of cells, hyperchromatic nuclei, nucleoli and foamy cytoplasm, $\times 470$

a number of smears and not be content with looking at one or two and counting 200 cells

Previous to this work, it had been my conception that when plasma cells were increased to 8 to 10 per cent and showed changes in their cytologic characteristics the diagnosis of myeloma was to be considered

first It would appear from the findings in this series of cases that such changes can occur in persons with certain chronic diseases such as carcinoma, and these results serve to emphasize again the importance of basing a diagnosis on the entire picture and not on just one feature

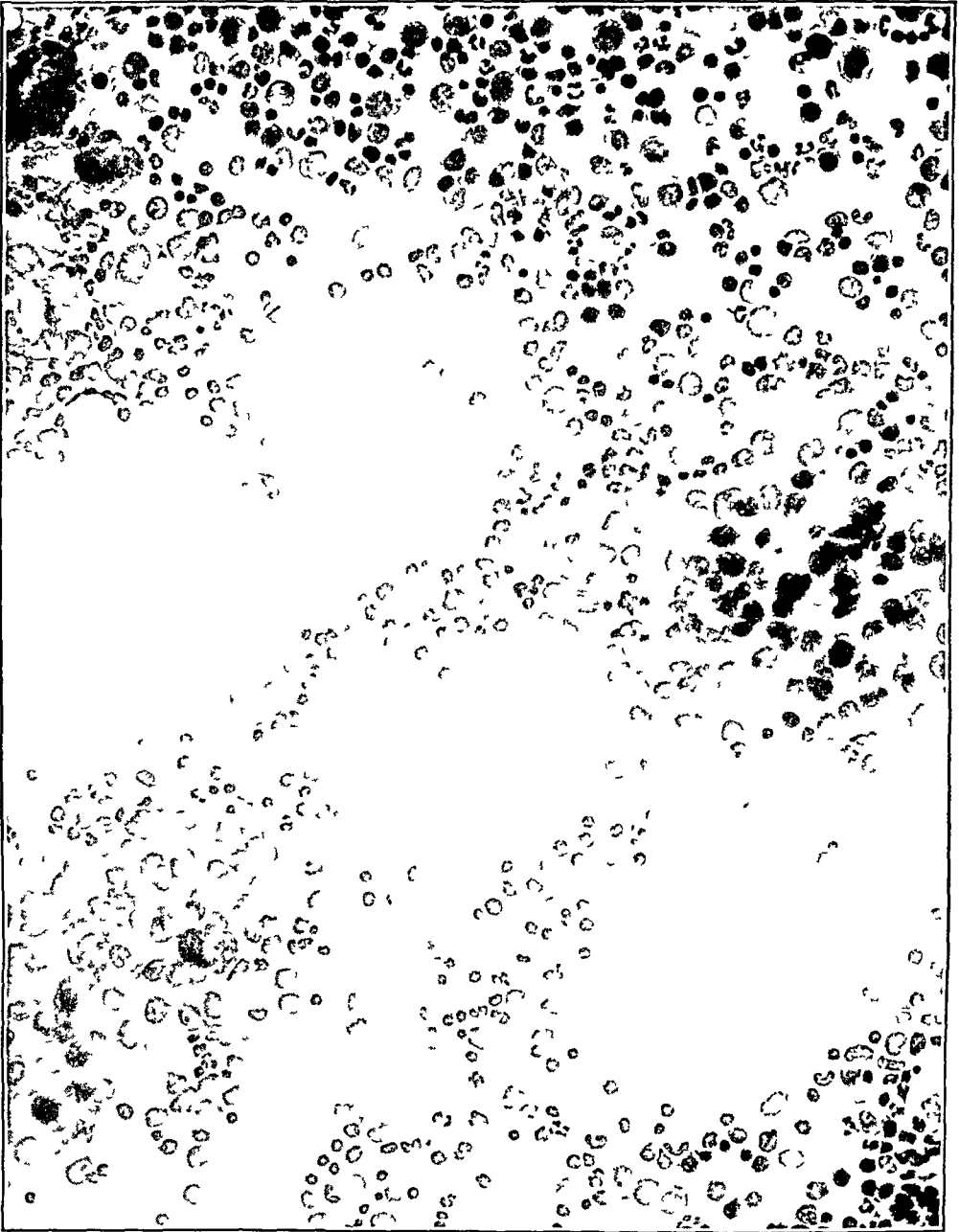


Fig 5 (case 15b) —Bone marrow These clumps of tumor cells were the only clumps found on the entire smear A megakaryocyte may be seen in upper left corner, $\times 220$

The finding of an increased number of eosinophilic cells in the bone marrow in the absence of other known causes for eosinophilia such as dermatitis, asthma or other allergic states, the presence of an increase in plasma cells and/or reticuloendothelial cells, the presence of single

atypical cells of undifferentiated character—any one or all of these should suggest the presence of a malignant tumor which has metastasized, and one may direct one's further efforts toward finding the primary site

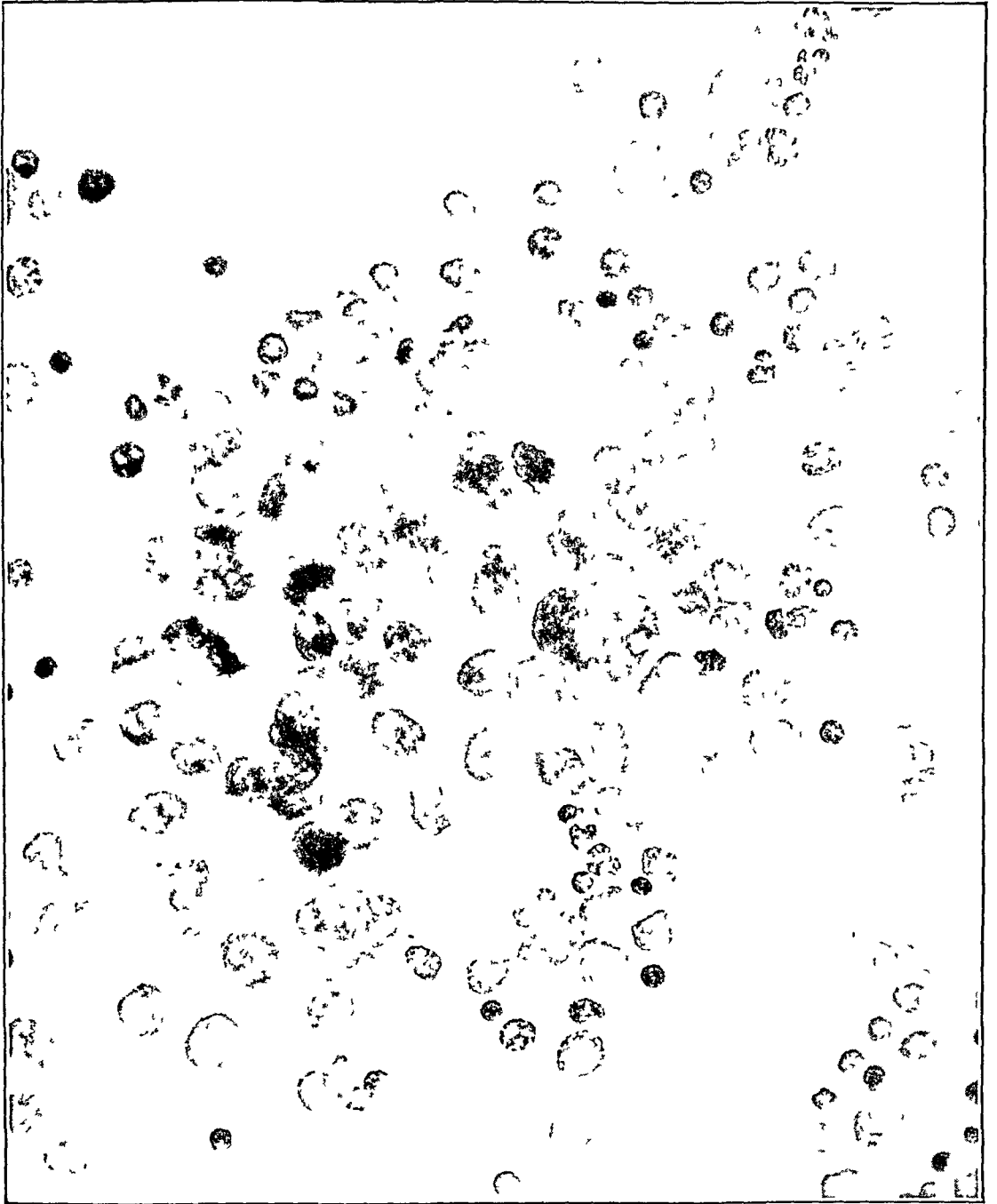


Fig 6 (case 15b) —High power magnification of one of tumor cell groups in figure 5. Foaminess of cytoplasm and nucleoli are especially well shown here. The tumor cells may be contrasted with normal myeloid cells shown in the upper right corner, $\times 470$

It should be pointed out again and reemphasized that unless the tumor cells occur in clumps and groups one cannot categorically make a definite diagnosis of metastases, but certainly the suggestive findings as

given could be valuable clues and aid in the further investigation of the patient

Most explanations for the anemia in patients with a malignant tumor have been based on the premise that the tumor cells have crowded out the normal erythroid elements. The figures cited in tables 2 and 3 raise the question again as to whether that is the answer, for it would appear that even in patients with anemia the percentage of erythroid elements in the bone marrow is within normal range

SUMMARY

A study of the bone marrow picture in 32 patients with metastatic cancer is reported

In 28 patients (87.5 per cent) there were deviations from accepted normal patterns in one or more respects

While actual tumor cells could be identified in the marrow of 25 per cent of the patients, other abnormal features were observed in a large percentage of preparations. Increase in number of plasma cells, reticuloendothelial cells, and/or eosinophilic elements certainly should suggest the presence of metastases

PROTOCOLS OF CASES

CASE 1—Mrs F K, a 44 year old Chinese woman had had a tumor the primary site of which was not definitely determined, it was thought to be a lung. Permission for autopsy was refused. Roentgenograms provided evidence of destruction of the twelfth rib and the transverse process of the first lumbar vertebra on the left

CASE 2—Miss E T, a 49 year old white woman, had undergone partial gastric resection for adenocarcinoma five years previously. There was roentgen evidence of widespread metastases to the pubis, spine, pelvis and femurs

CASE 3—Mrs M L, a 41 year old white woman, gave a history of removal of the right breast for carcinoma two years previously and recurrence in supra-clavicular nodes. Pathologic fracture of the right femur occurred, with roentgen evidence of metastases at the site of fracture

CASE 4—Mr A E, a 57 year old white man, had an adenocarcinoma of the left main stem bronchus diagnosed by roentgenograms and bronchoscopy with biopsy. It was thought to have metastasized because massive pleural effusions developed, but roentgenograms showed no evidence of metastases

CASE 5—Mr E L, a 49 year old white man, gave a history of grade 4 hemangioepithelioma which had been irradiated, with complete remission eleven years before. Roentgenograms showed opacity in the left upper pulmonary field, enlarged hilar nodes on the left and opacity in the stomach. Biopsy of a nodule in the neck was reported as showing anaplastic squamous cell carcinoma. At autopsy it was the pathologist's opinion that the primary site was probably a bronchus. There was no evidence of recurrence of the hemangioepithelioma

CASE 6—Mr S R, a 58 year old man presented roentgen evidence of destruction of the body of the second cervical vertebra at the site of an old fracture. After sternal aspiration a diagnosis of multiple myeloma was made. Since that time, further lesions demonstrable roentgenologically have developed

CASE 7—Mrs L H, a 48 year old woman, gave a history of grade 3 squamous cell carcinoma of the cervix, diagnosed by biopsy and treated with roentgen rays and radium. Jaundice, anorexia and nausea developed. A roentgenogram revealed extrinsic compression of the duodenum and an enlarged liver.

CASE 8—Mr H P, a 55 year old man, had a diagnosis of retroperitoneal reticulum cell sarcoma made by exploration and biopsy at operation. There was no roentgen evidence of metastases.

CASE 9—Mr P M, a 60 year old man, presented roentgen evidence of destructive lesions of the fourth thoracic vertebra and neurologic changes resulting from block demonstrated by operation at the level of the second thoracic vertebra. No satisfactory pathologic diagnosis was obtained. Roentgenograms showed some areas of decreased densities. A questionable diagnosis of multiple myeloma or metastatic carcinoma was made. Permission for autopsy was refused.

CASE 10—Mr M S, a 45 year old man, had adenocarcinoma of the stomach demonstrated roentgenologically and proved by exploration and operation. There was roentgen evidence of metastases to the spine.

CASE 11—Mr A P, a 60 year old man, gave a history of prostatic carcinoma of one and one-half years' duration. Roentgenograms gave evidence of an osteolytic process in the eleventh thoracic vertebra. Orchiectomy had been performed three days before sternal aspiration.

CASE 12—Mr D D, a 48 year old man, had an osteogenic sarcoma of the right tibia proved by biopsy and examination at amputation. There was no roentgen evidence of metastases. Sternal aspiration was done two days after amputation.

CASE 13—Mrs R K, a 26 year old woman with history of carcinoma of breast of one and one-half years' duration, had roentgen evidence of metastases to the spine and clinical evidence of possible metastases to the brain. Autopsy was not performed.

CASE 14—Mr R F, a 64 year old man, had a diagnosis of adenocarcinoma made from biopsy of a supraclavicular node, and tumor cells were found in ascitic fluid. There were physical signs and roentgen evidence of a pathologic process in the right lower pulmonary field. The primary site was not proved.

CASE 15—Mrs F H, a 64 year old woman with diagnosis of adenocarcinoma of the breast, had undergone radical mastectomy six and one-half years previously. There was roentgen evidence of metastases to the spine, ribs, femurs and sacrum.

CASE 16—Mr F H, a 57 year old man, had carcinoma of the colon diagnosed by roentgenograms and proved by exploration and biopsy. The liver and spleen were enlarged, but there was no roentgen evidence of other metastases.

CASE 17—Mr W M, a 52 year old white man, had a diagnosis of squamous cell carcinoma made by biopsy of a lymph node in the right axilla. Block at the level of the fifth thoracic vertebra and jaundice developed. Autopsy showed anaplastic carcinoma of the pancreas with multiple massive metastases to lymph nodes, liver, spleen, spine and ribs.

CASE 18—Mr T M was a 61 year old man with a mass in the left lumbar region, enlarged liver and spleen, osteolytic lesions in the left ilium, and an acid phosphatase level of 8 Armstrong units. Anaplastic carcinoma was diagnosed by biopsy of the ilium. The primary site was not diagnosed.

CASE 19—Mr S, a 65 year old man, had carcinoma of the prostate gland with roentgen evidence of metastases to the spine and pelvis.

CASE 20—Mrs A A, a 67 year old woman, with a diagnosis of adenocarcinoma of the cecum proved by exploration and biopsy, had no roentgen evidence of

metastases, but at operation it was noted that the tumor had extended to include the bladder and nodes removed

CASE 21—Mr E C, a 50 year old man, had an anaplastic carcinoma diagnosed by exploratory laminectomy The primary site had not yet been discovered

CASE 22—Mr J A., a 50 year old man with adenocarcinoma of the left kidney, diagnosed by pyelography and biopsy of a metastatic tumor mass in the left femur, had roentgen evidence of metastases to ribs The liver was enlarged

CASE 23—Miss O R, 55 years old, had carcinoma of the breast, first noted six years previously The diagnosis was proved by biopsy, and roentgen treatment was given There was roentgen evidence of metastases to the pelvis, skull and spine

CASE 24—Mrs A R, a 48 year old woman, had a distinctive lesion of the body of the seventh thoracic vertebra After sternal aspiration the diagnosis of multiple myeloma was made Additional lesions appeared, and Bence Jones protein was present for first time four months after the original diagnosis

CASE 25—Mr S d'A, a 22 year old man with osteogenic sarcoma of the right femur, proved by biopsy, had roentgen evidence of widespread metastases to the lungs, skull and left femur

CASE 26—Mr J L, a 55 year old man, had a history of massive gastrointestinal hemorrhage Roentgenograms revealed deformity of a large portion of the body of the stomach and the fundus The patient was not operated on and did not die in the hospital There was no roentgen evidence of other metastases

CASE 27—Mr W S, a 65 year old man, had a presumptive diagnosis of adenocarcinoma of the prostate gland Osteoplastic lesions of the body and wings of the sacrum were demonstrated two and one-half years before Cord bladder developed Recent roentgenograms gave evidence of extension of the lesions in the pelvis Orchiectomy produced clinical improvement

Case 28—Mr N F, a 48 year old man, had severe gradually developing macrocytic anemia and gastrointestinal symptoms of relatively short duration The primary site was not determined, whether stomach or pancreas

CASE 29—Mrs E B, a 49 year old woman with carcinoma of the cervix diagnosed by biopsy two years before, had been treated with roentgen rays There was no roentgenologic evidence of metastases, but anemia, pain in the lumbar area and neurologic symptoms in the lower extremities developed—all clinical symptoms of metastases by extension

CASE 30—Mr F Ha, a 58 year old man, had had a carcinoma of the stomach removed two years ago Although there was no roentgen evidence of metastases, there was clinical evidence of marked anorexia, weight loss and abdominal pain The patient died Autopsy confirmed the presence of widespread metastases

CASE 31—Mrs H C, a 68 year old woman, gave a history of "feeling sick" for three months and of rapid appearance of masses in the neck and left side of the abdomen Autopsy disclosed a massive tumor apparently primary in the left kidney with widespread metastases throughout the body

CASE 32—Mrs J S, a 76 year old woman, gave a history of radical mastectomy (excision of the right breast) for adenocarcinoma three years previously Anemia was noted in March, three months before her admission

Dr Robert S Evans gave advice in the performance of this study Miss Rose T Duane gave technical assistance Physicians of the staff of Stanford University Hospitals and the United States Marine Hospital, San Francisco, made cases available for this study

MOTOR MANIFESTATIONS OF HERPES ZOSTER

Report of a Case of Associated Permanent Paralysis of the Phrenic Nerve

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HERPES zoster is a nervous disorder which is usually associated with dermatologic manifestations. It was the latter which gave the disease its name, since its external manifestations were known to the ancients. Herpes is a generic term which has been applied to numerous dissimilar acute inflammatory reactions of the skin and, as such, is misleading. We shall omit it during the rest of the present paper and shall refer to the disease entity under discussion as zoster. This latter term comes from the Greek *ζωστήρ* and refers to the fact that the disease when leading to dermatologic manifestations on the trunk spreads around it like a girdle. Though zoster is not an accurate term, the disease denoted is evident, therefore, this nomenclature is utilized in the present report.

That zoster is a nervous disorder was established by pathologic examination in 1862¹. Its neuropathology was established on a firm foundation in 1900 by Head and Campbell². Motor phenomena as a manifestation of the process were described in 1866³. That the anterior horn was probably frequently involved even though no external paralysis was present was not made evident until 1924,⁴ but the fact has been verified since that time⁵. That the disease is of viral origin has been

1 von Baresprung, F G F. *Fernere Beitrage zur Kenntniss des Zoster*, Ann d Char-Krankenh zu Berlin **10** 37, 1862

2 Head, H, and Campbell, A W. *The Pathology of Herpes Zoster and Its Bearing on Sensory Localization*, Brain **23** 353, 1900

3 Broadbent, W H. *Case of Herpetic Eruption in the Course of Branches of the Brachial Plexus Followed by Partial Paralysis in Corresponding Motor Nerves*, Brit M J **2** 460, 1866

4 Lhermitte, J, and Nicolas, M. *Les lésions spinales du zona. La myélite zostérienne*, Rev neurol **31** 361, 1924

5 (a) Denny-Brown, D, Adams, R D, and Fitzgerald, P J. *Pathologic Features of Herpes Zoster. A Note on "Gemiculate Herpes,"* Arch Neurol & Psychiat **51** 216 (March) 1944. (b) Adams, R D. *The Pathological Features of Herpes Zoster*, Bull New England M Center **6** 12, 1944. (c) Riggs, H E, and Rupp, C. *Pathological Changes in Early Herpes Zoster*, J Neuropath & Exper Neurol **7** 100, 1948

conclusively established, the organism probably being closely related to, though not identical with, the virus of varicella⁶ On reaching the nervous system, probably as an ascending myelitis, the virus causes diffuse damage, as noted later in this report It usually attacks one or two segments, most vigorously destroying the posterior ganglion on that level, and travels down to the skin to cause the characteristic eruption⁷ According to the extent of damage in the different areas of the nervous tract, other manifestations become apparent These have formerly been referred to in the literature as "complications," but they should not be called such, since they are part and parcel of the disease process, just as paralysis is an integral part of the manifestations of acute anterior poliomyelitis This paper is concerned only with the motor manifestations of the essentially neurologic disorder zoster A manifestation heretofore not reported is also presented and discussed

MOTOR SYMPTOMS

Though the latest textbooks of medicine, dermatology and neurology, as well as recent reviews,⁸ refer to motor symptoms as a rare complication, in 1916 Weber⁹ had already noted that there was "a large literature in regard to herpes zoster associated with muscular paresis and muscular atrophy" He described a case with paralysis of the arm and 1 with oculomotor paresis and paralytic mydriasis Lesions of the upper motor neuron are usually due to lesions in the brain The former are rare, may present as a hemiplegia and are often fatal Lower motor neuron pareses are relatively common and may involve either the cranial or the spinal nerves They are almost always associated with a herpetic eruption, but zoster paresis without dermatologic manifestations has been reported¹⁰

Oculomotor paresis is common and is usually associated with zoster ophthalmicus, but not invariably so There may be a single muscle involved, or all the muscles supplied by the third, fourth and sixth cranial nerves may be paretic Of 2,250 cases of ophthalmic zoster

6 Stokes, J, Jr Varicella-Herpes Zoster Group, in Rivers, T M *Viral and Rickettsial Infections of Man*, Philadelphia, J B Lippincott Company, 1948, chap 23, p 395

7 Stern, E S Mechanism of Herpes Zoster and Its Relationship to Chicken-Pox, *Brit J Dermat* **49** 263, 1937 Montgomery, D W Herpes Zoster as a Primary Ascending Neuritis, *Arch Dermat & Syph* **4** 812 (Dec) 1921

8 Baird, P C, Jr Herpes Zoster, *New England J Med* **228** 568, 1943

9 Weber, F P Herpes Zoster Its Occasional Association with a Generalized Eruption and Its Occasional Connection with Muscular Paralysis, *Internat Clin* **3** 185, 1916

10 (a) Aitken, R S, and Brain, R T Facial Palsy and Infection with Zoster Virus, *Lancet* **1** 19, 1933 (b) Spillane, J D Bell's Palsy and Herpes Zoster, *Brit M J* **1** 236, 1941

recorded by Edgerton up to 1942, ocular muscles were involved in 13 per cent¹¹ The third nerve is most frequently involved, there being partial or total ptosis or mydriasis Abducens paralyses occur less frequently, and isolated paralysis of the trochlear nerve is the least common A combination of paralyses of any two ocular nerves may be present, there are recorded 40 cases of simultaneous paralysis of the third, fourth and sixth nerves There are only 2 cases of bilateral paralysis recorded in the literature, one of bilateral paralysis of the third nerve and one of bilateral paralysis of the sixth nerve¹² The paresis most often occurs after the eruption and is transient, lasting up to several months It may be permanent The production of a nuclear lesion is probably due to extension of the virus infection, either to the motor nerve or to the neuraxis

Facial palsy is perhaps the commonest of the motor lesions Until recently it was thought, because of the work of Hunt,¹³ who originally described the syndrome of facial palsy with zoster, that the geniculate ganglion was always involved The facial nerve was also involved in 7 per cent of cases of ophthalmic zoster and in certain cases of cervical zoster It was felt that in those cases in which there were no cutaneous lesions in the seventh nerve distribution the ganglion cells were sufficiently involved to have produced paresis without herpes This concept has been disproved by the work of Denny-Brown and his associates^{5a} and by that of O'Neill¹⁴ The former showed pathologically that lesions of the geniculate ganglion do not necessarily accompany the facial palsy In many of O'Neill's cases there was no herpes or other evidence of involvement of the geniculate ganglion but there was clearcut involvement of one or several other cranial ganglions or cervical segments In these instances the infection involves the nerve or motor nuclei but the sensory apparatus remains unaffected Like other types of motor paresis associated with zoster, facial palsy usually is transient, lasting weeks to months, but may be permanent

Motor paralysis of spinal root distribution has been reported less commonly, reasons for this will be discussed later in this report Broad-

11 Edgerton, A E Herpes Zoster Ophthalmicus Report of Cases and a Review of the Literature, *Tr Am Ophth Soc* **40** 390, 1942

12 de River (1925) and Gallois (1924), cited by Edgerton¹¹

13 Hunt, J R Herpetic Inflammations of the Geniculate Ganglion A New Syndrome and Its Complications, *J Nerv & Ment Dis* **34**:73, 1907, *Arch Otol* **36** 371, 1907, Further Contributions to the Herpetic Inflammations of the Geniculate Ganglion, *Am J M Sc* **136**:226, 1908, Herpetic Inflammations The Symptom-Complex of Acute Posterior Poliomyelitis of the Geniculate, Auditory, Glossopharyngeal and Pneumogastric Ganglia, *Arch Int Med* **5** 631 (June) 1910

14 O'Neill, H Herpes Zoster Auris ("Geniculate Ganglionitis"), *Arch Otolaryng* **42**:309 (Nov-Dec) 1945

bent³ first discussed this feature in 1866 when he reported a case of zoster of the arm and neck in which paralysis of the corresponding motor nerves of the brachial plexus developed. The subject was discussed by Carter and Dunlop¹⁵ and by Taterka and O'Sullivan¹⁶. The latter reported 44 cases, including the 2 of Carter and Dunlop. There were 20 cases of paralysis of the upper extremity, 18 of paralysis of the muscles of the trunk and 6 of paralysis of the lower extremities. Since then, cases have been reported by Abercrombie,¹⁷ Gordon and Tucker,¹⁸ Parkinson,¹⁹ Michaux, Granier and Lacourbe,²⁰ Lemmon²¹ and Rosow.²² Brain's case of pseudodiaphragmatic hernia²³ should also be included. In Abercrombie's case there was paralysis of the anterior tibial muscles corresponding to lesions of the fourth and fifth lumbar segments, whereas sensory changes in the leg and foot corresponded to the first and second sacral segments and the dermatologic reaction to the third sacral segment, thus showing diffuse motor and sensory involvement of the lower lumbar and the upper sacral segments. In the first case of Gordon and Tucker, there was muscular weakness and cutaneous involvement of the second and third lumbar segments in addition to facial involvement, in their second case, there was right hemiplegia. Parkinson's case showed both rash and paralysis in the distribution of the fifth cervical segment. Michaux's case involved the brachial plexus, in Lemmon's there were weakness and atrophy of the muscles supplied by the fifth and sixth cervical segments and in Rosow's case paralysis of the right deltoid muscle, paresis of the muscles of the right upper arm and forearm, slight weakness of the trapezius muscle and atrophy of the supraspinatus muscle and the thenar eminence. Our unusual case is described in detail in this paper.

15 Carter, A. B., and Dunlop, J. B. W. Paresis Following Herpes Zoster. A Report of Two Cases, *Brit M J* **1** 234, 1941.

16 Taterka, J. H., and O'Sullivan, M. E. Motor Complications of Herpes Zoster, *J A M A* **122** 737 (July 10) 1943.

17 Abercrombie, R. G. Herpes Zoster with Muscular Paralysis and Disturbance of Sensation, *Brit M J* **1** 778, 1941.

18 Gordon, I., and Tucker, J. F. Lesions of the Central Nervous System in Herpes Zoster, *J Neurol, Neurosurg & Psychiat* **8** 40, 1945.

19 Parkinson, T. Rarer Manifestations of Herpes Zoster, *Brit M J* **1** 8, 1948.

20 Michaux, L., Granier, and Lacourbe, R. Paralysie postzosterienne a type radiculaire supérieur du plexus brachial, *Rev neurol* **75** 154, 1943.

21 Lemmon, G. B., Jr. Herpes Zoster with Motor Involvement. Report of a Case, *U S Nav M Bull* **43** 357, 1944.

22 Rosow, H. M. Herpes Zoster with a Motor Complication, *M Bull Vet Admin* **20** 350, 1944.

23 Brain, W. R. *Diseases of the Nervous System*, ed 2, New York, Oxford University Press, 1940, p 465.

These cases of motor paresis have no particular pattern. In about 75 per cent of cases the eruption appears a few days to a few weeks before the paralysis, and in most of the remainder the paresis appears prior to the eruption, though at times the appearance of the symptoms is simultaneous. The percentage of cases without eruption is probably small but is indeterminate. To find the exact number, in every case of facial palsy, of oculomotor paresis or of other muscular paresis of unknown origin a lumbar puncture should be performed and complement fixation studies made. This probably should be done in all cases of these conditions which are associated with neuralgias. The motor lesions are invariably on the same side as the cutaneous and neuralgic manifestations, but in about one fifth of the cases the segments do not correspond. The paralysis may be permanent, there may be partial recovery or there may be complete recovery, depending on the severity and irreversibility of the damage to the anterior horn cells, the cranial nuclei or the nerve fibers involved.

PATHOLOGY

Von Barenprung¹ first described the inflammatory changes in the dorsal root ganglion and in related portions of the spinal nerve. Head and Campbell² also demonstrated the lesions of the affected ganglion. They showed patchy inflammation of the neighboring ganglion and nerves, including the motor nerve root, and stated the belief that changes in the posterior roots and horns were secondary and degenerative. The papers of the French school of Lhermitte and his various collaborators²⁴ indicated more diffuse involvement. The patient of Lhermitte and Nicolas⁴ died seven weeks after an acute attack of zoster. Pathologic examination of the spinal cord showed marked evidence of inflammatory changes in the anterior horns. In this case, as in most of the others noted in the remainder of this section, there was no record of a motor lesion clinically. Wohlwill²⁵ also noted extensive inflammatory changes in the central nervous system. Denny-Brown and others^{5a} and Adams^{5b} reported on 3 cases in which death occurred, due to various causes, within a few days to a few weeks after an attack of herpes. They observed, in addition to ganglionitis marked by pannecrosis of all or part of the ganglion, poliomyelitis involving both the anterior and the posterior horns and roots, relatively mild localized leptomeningitis and

24 Lhermitte and Nicolas⁴ Lhermitte, J, and Vermès. Les lésions du système nerveux central dans le zona, *Rev. neurol.* **1** 1231, 1930. Faure-Beaulieu, M, and Lhermitte, J. Les lésions médullaires du zona idiopathique. La myélite zostérienne, *ibid.* **1** 1250, 1929.

25 Wohlwill, F. Zur pathologischen Anatomie des Nervensystems beim Herpes Zoster, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **89** 171, 1924.

true peripheral mononeuritis in the nerves distal to the ganglion and in the anterior nerve root. The characteristic histopathologic picture of neurotropic virus infections was seen. The patient of Riggs and Rupp,²⁶ who died suddenly on the third day of the disease from peripheral vascular collapse twenty minutes after the administration of a paravertebral block with procaine hydrochloride (novocain®) also showed diffuse involvement of the spinal cord. The almost constant finding of a moderate increase in cells in the cerebrospinal fluid in cases of zoster and the frequent occurrence of a slight excess of protein are also indicative of involvement of the cord. In addition to involvement of the meninges, the brain stem and the cortical tissue proper have been found to be affected in a number of cases.

CORRELATION OF PATHOLOGIC AND CLINICAL PICTURES

The variegated clinical pattern manifested in zoster is easily comprehended if one takes a quantitative point of view regarding the pathologic changes. The severity of the lesion in various locations determines the symptomatology. What factors decide the special localization and distribution of the lesions has not been determined. The facts that some patients show no paresis even though involvement of the anterior horns is present and that the paresis may be transient or permanent raise the questions of the extent of the lesion necessary to produce paresis and of the basis of the temporary nature of the palsy in a large percentage of cases. The answer seems to be that not all the anterior horn cells are necessary for apparently normal function. This has been shown experimentally in monkeys²⁶ and is clear from the cases described previously and from the extensive work in anterior poliomyelitis.²⁷ Since in the majority of cases only one or two segments are primarily and extensively involved, the segmental distribution may be such that the major innervation of a given muscle is not affected, also, certain muscles are supplied by more than one nerve. It is possible, since many muscles are members of a group functioning as a unit, that dysfunction of one muscle may go unrecognized unless specific tests of its condition are made. This is especially true in zoster, in which the dramatic dermatologic and neuralgic manifestations usually lead the patient to a dermatologist or a general practitioner. These physicians are preoccupied

26 Sabin, A. B., and Ward, R. Nature of Non-Paralytic and Transitory Paralytic Poliomyelitis in Rhesus Monkey Innoculated with Human Virus, *J Exper Med* **73** 757, 1941.

27 Bodian, D., and Howe, H. A. Pathology of Early Arrested and Non-paralytic Poliomyelitis, *Bull Johns Hopkins Hosp* **69**:135, 1941. Sabin, A. B. Pathology and Pathogenesis of Human Poliomyelitis, *J A M A* **120** 506 (Oct 7) 1942.

with the cutaneous and sensory manifestations, and only a frank paresis is usually noted, transient minor motor symptoms or those involving the cord going unobserved. The damage to the neurons or motor fibers is undoubtedly reversible in most instances, as with other virus diseases.

One of us (S. L. H.) had occasion recently to see a patient who had had zoster involving apparently the fourth and fifth cervical segments. He stated that he had had some weakness of the arm during the period of the illness. When he was seen, there was no evidence of motor involvement or of other neurologic disturbance. Whether this case represented true paresis is a matter of conjecture at the time of this report since no neurologic tests of any nature were performed at the time of the symptoms, the weakness, when mentioned, having been casually attributed to the neuralgia by the attending physician, though the patient stated that the disappearance of the neuralgia antedated by a few days the recovery of full strength in the arm.

REPORT OF CASE

The following case, in which permanent paralysis of the phrenic nerve occurred with zoster, is reported in detail since it has no parallel in the literature.

W. H., a white man of 53, was in excellent health until June 1947. He had lived in Massachusetts all his life, had never had chickenpox or other childhood diseases, had never been vaccinated or received any immunizations and had had no operations or venereal disease. The patient had had no illnesses that year, nor had he a history of exposure to zoster or varicella. Ten days after his acting as a blood donor, the right arm having been used, an excruciatingly painful vesicular eruption began to develop. This blossomed out as a typical zoster involving the third and fourth cervical segments on the right side. It was associated with regional lymphadenopathy. Three days after the eruption reached its maximum shortness of breath developed. This was not associated with cough or pain in the chest. The patient could breathe with greater facility when lying on his right side. A general physical examination was reported as noncontributory. The patient received symptomatic treatment for his eruption, ointments were applied locally and penicillin was given intramuscularly. After ten to fourteen days the eruption began to dry up, and it eventually cleared, except for some residual scars. However, exertional dyspnea persisted. The patient was treated variously for a neurasthenic disorder and for potential cardiac disease, receiving sedatives. On June 8, 1948 he was seen by one of us (A. H. C.). The patient was well developed. He had no palpitation, sweating, dizziness or other symptoms of neurasthenia. His only complaint was of dyspnea, especially on exertion but also after meals and on bending over. A diagnosis of paralysis of the right side of the diaphragm was made. Complete examinations (by S. L. H.) at that time and almost eleven months later, on March 20, 1949, revealed essentially the same physical findings. These consisted of scars in the region of the third and fourth cervical dermatomes on the right side, a slightly raised right side of the diaphragm which failed to descend on deep inspiration and a positive Hoover sign. Examination of the heart, lungs, abdomen, extremities and general nervous system was

noncontributory Fluoroscopic examination revealed paralysis of the diaphragm on the right side It behaved paradoxically, rising on inspiration and descending on expiration (the Kienbock phenomenon), this being noted especially on sniffing There was no evidence on roentgenologic or fluoroscopic examination on either occasion of any pathologic features in the heart or lungs, and no masses were visible in the roots of the lungs or in the paramediastinal structures There was no evidence of destruction of bone in the cervical portion of the spine, of narrowed intervertebral disk spaces or of abnormal articular facets The roentgen appearance of the soft tissue of the cervical portion of the spine was normal A gastrointestinal work-up revealed no paralysis of the swallowing reflex, no evidence of compression, dilatation or other abnormalities in the esophagus or in the remainder of the gastrointestinal tract and no signs of hiatus hernia Electrocardiograms were within normal limits, as was the basal metabolic rate The complete blood count and the blood sugar and nonprotein nitrogen revealed no abnormalities The urinalysis was noncontributory The vital capacity and the maximum breathing capacity were diminished The ventilation equivalent for oxygen was normal

The diagnosis was therefore made of exertional dyspnea due to paralysis of the diaphragm secondary to paralysis of the phrenic nerve associated with zoster This diagnosis was justified by the concomitant onset of the two processes, the association of spiral segments in the two conditions and the failure to find any other cause for paralysis of the phrenic nerve and the diaphragm or for symptomatic dyspnea There was no improvement in the patient's condition during the time of observation Since the paralysis was of almost two years' duration at the time of writing, it is felt that it can be classified in the permanent category

COMMENT

The phrenic nerve is the chief and probably the only motor nerve for the diaphragm²⁸ It arises from the third and fourth cervical segments and also receives fibers from the fifth cervical segment Its paralysis leads to diaphragmatic paralysis Thus, disturbances of respiration can result from lesions in the third to fifth cervical segments, which involve the anterior horn cells of the phrenic nerve²⁹

Paralysis of the phrenic nerve resulting in paralysis of a hemidiaphragm is not infrequent It may be caused by disease processes which involve the cervical portion of the cord (such as poliomyelitis), by neuritis from diphtheria or lead poisoning or by injuries to the cervical portion of the cord or to the phrenic nerve and by tumors in the mediastinum or the region of the neck, by an aneurysm of the aorta or by matted lymph nodes in the mediastinum, all of which can injure the phrenic nerve by compression The paralyzed diaphragm subsequently thins out

28 Schlaepfer, K The Phrenic as the Nerve of Motor Innervation of the Diaphragm, *Bull Johns Hopkins Hosp* **34** 195, 1923

29 Bing, R *Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord*, translated and edited by W Haymaker, ed 11, St Louis, C V Mosby Company, 1940

and becomes fibrous. Its failure to function in respiration causes an impairment of the ventilatory mechanism of the lungs and so may lead to dyspnea, especially on exertion. Tests for pulmonary function in the present case confirmed the presence of this process as the cause of the exertional dyspnea. It is interesting to note the shortness of breath after eating a full meal and on bending over. Each of these activities served to fix the left side of the diaphragm, thus causing further limitation of the vital capacity, which was already restricted by paralysis of the right side of the diaphragm.

Paralysis of the phrenic nerve as a motor manifestation of zoster has not previously been reported in the literature. Similarly, this is the first case of phrenic paralysis due to involvement of the nuclear region of the phrenic nerve by the zoster virus. The mechanism was similar to that of paralysis of the phrenic nerve associated with anterior poliomyelitis. All possible other etiologic mechanisms of diaphragmatic paralysis were excluded. This, plus the temporal sequence after the attack of zoster and the fact that the zoster did involve at least the third and fourth cervical segments, as evidenced by the cutaneous lesions, makes the relationship between the infection with zoster virus and the paralysis of the phrenic nerve conclusive. Whether the infection was introduced during the venipuncture when the patient served as a blood donor could not be judged.

CONCLUSIONS

Involvement of the motor nervous system by zoster, either through attacking the anterior horn or the cranial nuclei or through actual disease of the nerves is not at all unusual, as manifested by pathologic studies. Despite the frequent involvement of the anterior gray matter, motor manifestations are not usually detected with the anticipated frequency. The reasons for this discrepancy are discussed in the section on correlation of the pathologic and clinical picture. It is important that every patient with zoster be scrutinized for motor manifestations, especially should the muscles innervated by the affected segments be routinely tested. This procedure would serve several purposes. First, the true incidence of motor manifestations would become known, second, criteria for diagnosing those unusual cases of muscular paresis, with or without neuralgias, which are due to *zoster sine herpete*³⁰ might possibly be established, third, errors in diagnosis would be avoided—for example, the case reported here could have been diagnosed properly at its onset had these considerations been thought of, and, fourth, a more accurate concept of the pathogenesis and nature of zoster would emerge from more careful clinical observations.

SUMMARY

1 Motor manifestations are an integral part of the neurodermatologic disorder zoster and are a result of the basic pathologic process

2 Motor symptoms, especially those of a mild and transitory nature, occur frequently and will be found more frequently if specifically looked for

3 Permanent destruction of motor neurons in the anterior horns or of the nuclei of origin of the motor cranial nerves may result in permanent paralysis

A case is presented in which permanent paralysis of the phrenic nerve resulted after an attack of zoster

Q FEVER IN A VETERANS' HOSPITAL

R W BRAWLEY, M D

AND

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VAN NUYS, CALIF

Q FEVER as a new disease entity was first recognized and reported by Derrick¹ in 1937. He stated that the first case of this disease probably occurred in Queensland, Australia, in 1933. Davis and Cox² recognized and described the first case in the United States, and they termed the disease "nine mile fever" because of its occurrence in Nine Mile Creek, Mont. Since that time, numerous outbreaks of the disease in various parts of the United States, Panama and Italy have been described.³ The demonstration of specific antibodies in the blood of persons living in Idaho, Montana, Wyoming, Nebraska, Nevada, Arizona

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1 Derrick, E H. "Q" Fever. A New Disease Entity, Clinical Features, Diagnosis and Laboratory Investigation, M J Australia **2**:281-299, 1937

2 Davis, G E, and Cox, H R. A Filter-Passing Infectious Agent Isolated from Ticks, Pub Health Rep **53** 2259-2267, 1938

3 (a) Robbins, F C, and Ragan, C A. Q Fever in Mediterranean Area. Report of Its Occurrence in Allied Troops, Am J Hyg **44**:6, 1946. (b) A Laboratory Outbreak of Q Fever Caused by the Balkan Grippe Strain of Rickettsia Burneti, Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina, *ibid* **44** 123-157, 1946. (c) Feinstein, M, Yesner, R, and Marks, J L. Epidemics of Q Fever Among Troops Returning from Italy in the Spring of 1945. Clinical Aspects of the Epidemic at Camp Patrick Henry, *ibid* **44** 72-87, 1946. (d) Shepard, C C. An Outbreak of Q Fever in a Chicago Packing House, *ibid* **46** 185-191, 1947. (e) Huebner, R J, Jellison, W L, Beck, M D, Parker, R R, and Shepard, C C. Q Fever Studies in Southern California, Pub Health Rep **63** 214-222, 1948. (f) Irons, J V, and Hooper, J M. Q Fever in the United States. Clinical Data on an Outbreak Among Stock Handlers and Slaughterhouse Workers, J A M A **133** 815-818 (March 22) 1947. (g) Huebner, R J. Report of an Outbreak of Q Fever at the National Institute of Health, Am J Pub Health **37** 431-440, 1948. (h) Cheney, G, and Geib, W A. The Identification of Q Fever in Panama, Am J Hyg **44** 158-172, 1946. (i) Hornbrook, J W, and Nelson, K R. An Institutional Outbreak of Q Fever, Pub Health Rep **55**:1936-1945, 1940

and Washington ⁴ and the natural occurrence of epidemics in Texas,⁵ Illinois ^{3d} and California ^{3g} attest to the widespread distribution of this disease in the United States. Numerous laboratory outbreaks among technicians working with this rickettsial organism have also been reported ⁶. From 1937 to 1944 more than 217 cases were reported in Australia ⁷. More than 200 cases of Q fever with positive diagnosis have been observed in Los Angeles County during the past year. Prior to this recent epidemic in California most of the cases described have occurred in laboratory technicians, meat workers and dairy farmers.

The causative agent of Q fever was first isolated by Burnet in Australia ⁸ and was given the name *Rickettsia burneti* by Derrick. He identified the typical rickettsial bodies in sections and smears of infected mouse livers and spleens. Cox ⁹ isolated the organism first in America, and suggested the name "*Rickettsia diaporica*." However, Burnet and Freeman ¹⁰ showed that the rickettsia isolated by Cox was immunologically indistinguishable from the rickettsia of Australian Q fever. Recently the name *Coxiella burneti* has been suggested and accepted for this causative organism. *C. burneti* (*diaporica*) is a minute, gram-negative, pleomorphic organism that occurs both intracellularly and extracellularly in affected tissues. It stains well with Giemsa stain and passes through N and W Berkefeld filters but fails to pass through a single Seitz disk ⁹.

The mode of transmission of this disease has not been definitely ascertained. That cattle serve as a reservoir of the organism has been definitely established. That the agent is highly infectious has been shown by the high incidence of infection among persons known to have been exposed. As previously noted the incidence is highest in those engaged as dairy farmers or meat handlers. Whether a parasite may serve as the vector in transmission is still being investigated. *C. burneti* has

4 Strong, R. P. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed 7, Philadelphia, The Blakiston Company, 1944.

5 Topping, N. A., Shepard, C. C., and Irons, J. V. Q Fever in the United States. Epidemiologic Studies of an Outbreak Among Stock Handlers and Slaughterhouse Workers, J. A. M. A. **133** 813-815 (March 22) 1947.

6 Burnet, F. M., Freeman, M., Derrick, E. H., and Smith, D. J. W. The Search for Immunological Relationship Between "Q" Fever and Other Rickettsioses, M. J. Australia **2** 51-54, 1939. Footnote 3 a, b and c.

7 Derrick, E. H. The Epidemiology of Q Fever, J. Hyg. **43** 357-361, 1944.

8 Burnet, F. M., and Freeman, M. Experimental Studies on the Virus of Q Fever, M. J. Australia **2** 299-305, 1937.

9 Cox, H. R. *Rickettsia Diaporica* and American Q Fever, Am. J. Trop. Med. **20** 463-469, 1940.

10 Burnet, F. M., and Freeman, M. A Comparative Study of Rickettsial Strains from an Infection of Ticks in Montana (U. S. A.) and from Q Fever, M. J. Australia **2** 887-891, 1939.

been isolated from ticks in several parts of the United States¹¹ Huebner^{3g} failed to transmit the disease to guinea pigs by the injection of ground insects and other arthropods found on or in the vicinity of infected cows Derrick¹ stated that the blood and urine of diseased guinea pigs would transmit the infection, however, Huebner^{3g} failed to transmit the disease to guinea pigs inoculated with blood, urine or feces of diseased cows From 10 to 20 per cent of the dairy cows in the Los Angeles area possess significant serum antibodies for Q fever, but no perceptible illness is noted in these animals^{3g} In a laboratory outbreak of Q fever, 9 of 11 technicians in one room engaged in culturing the organism contracted the disease The 2 who remained healthy were the only workers who wore masks while engaged in this work^{3b} This incident points to the possibility of air-borne transmission of the infective agent Epidemiologic studies of an outbreak among stock handlers and slaughterhouse workers in Texas also cast suspicion on the air-borne mode of transmission This mode of transmission with subsequent inhalation of the organism has been suggested by recent investigations in Los Angeles County^{3g} The inhalation of dust contaminated with droplets of infected cows' milk wasted during the process of milking may be involved in this mechanism The disease is probably not transmitted by ingestion of milk, and pasteurization apparently renders milk non-infectious No instance of transmission of the disease from person to person has been noted

The pathologic changes caused by Q fever in man have not been adequately described The mortality rate is very low, and in those patients who died of this disease the diagnosis was not suspected and the pathologic changes were not adequately observed In a fatal human case reported by Lillie, Perrin and Armstrong,¹² the gross pathologic abnormalities were pulmonary edema and congestion, a firm granular consolidation of the upper lobe of the right lung posteriorly and a large soft spleen Much fibrin and a moderate mononuclear cell reaction were observed microscopically in the alveoli and bronchioles, however, the rickettsia was not demonstrated histologically These authors noted similar pathologic changes in the Rhesus monkey Longcope¹³ in 1940 published in detail the pathologic findings in 2 autopsy cases of bronchopneumonia of unknown cause It is probable that these deaths were due

11 Parker, R R, and Kohls, G M American Q Fever The Occurrence of Rickettsia Diaporica in Amblyomona Americanum in Eastern Texas, Pub Health Rep 58 1510-1511, 1943 Davis and Cox²

12 Lillie, R D, Perrin, T L, and Armstrong, C Institutional Outbreak of Pneumonitis Histopathology in Man and Rhesus Monkeys in the Pneumonitis Due to the Virus of "Q" Fever, Pub Health Rep 56 149-155, 1941

13 Longcope, W T Bronchopneumonia of Unknown Etiology (Variety X) A Report of Thirty-Two Cases with Two Deaths, Bull John Hopkins Hosp 67 268-305, 1940

to Q fever. However the diagnosis cannot be accepted with certainty, as it was not confirmed by any established laboratory procedure. Recently, in Los Angeles County, autopsy in a case of suspected Q fever revealed lobar pneumonia of a fibrinous type with focal hemorrhages into the alveolar spaces. The microscopic picture consisted in an infiltration of round cells, giant cells and mononuclears with an almost complete absence of polymorphonuclears.¹⁴ Large friable spleens and subcutaneous indurated nonsuppurative inflammatory reactions were noted grossly in infected guinea pigs.^{3e} Parker and Kohls¹¹ noted similar changes in guinea pigs and also observed that the lymph nodes were enlarged and injected. The gross pathologic observations at autopsy in a fatal case of Q fever have recently been described by Brown, Knight and Jellison.¹⁵

It is generally accepted that one attack of Q fever confers immunity of indefinite duration. In controlled studies, it was noted that one laboratory infection in guinea pigs confers a permanent immunity.¹ This immunologic response is utilized in establishing the diagnosis of Q fever in human beings. No cross immunity with other rickettsial infections has been noted.⁹ Serum from patients or animals suffering from most of the known rickettsioses give a negative agglutination reaction with emulsions of *C. burnetii*. The persistence of immunity may be partially related to the observation in experimental animals that the infectious agent may be recovered from the spleen, liver, lungs, brain, testes and seminal vesicles at least one hundred days or more after inoculation.¹⁶ Corroborating evidence of the immunity conferred by Q fever will be noted later, when diagnostic tests and possible prophylactic vaccination are considered.

CLINICAL FEATURES OF Q FEVER

We have observed 12 cases of Q fever with positive serologic diagnoses during the past year. It must be borne in mind that the clinical features of Q fever as presented here are those of cases in which the symptoms are severe enough to necessitate hospitalization. As it can be assumed that all persons who show a positive serologic reaction for Q fever have been exposed to infection by *C. burnetii*, it may be concluded, since these persons give no history of any symptoms that may have been a manifestation of disease, either that in the majority of cases of Q fever there are no symptoms or that symptoms similar to those of an acute infection of the upper respiratory tract are so mild as to pass unnoticed.

14 Denlinger, R. B. Unpublished data.

15 Brown, D. C., Knight, L. A., and Jellison, W. L. A Fatal Case of Q Fever in Southern California, *California Med* 69:200-203, 1948.

16 Parker, R. R., and Steinhaus, E. A. American and Australian Q Fever. Persistence of the Infectious Agents in Guinea Pig Tissues After Defervescence, *Pub. Health Rep* 58:523-527, 1943. Davis and Cox.²

All our patients were Caucasians, and all were men. Their ages ranged from 23 to 47 years. Most of the patients with acute infectious diseases seen at this hospital are in this age group. The disease has been diagnosed in patients from 3¹⁴ to 68³⁵ years of age. Proximity to dairies by reason of occupation or residence was regarded as a common factor in the histories of 50 per cent of the patients seen in this country³⁶. Three of our patients worked in dairies, 6 lived in the neighborhood of milk farms. One patient was bitten by a cat four days prior to the onset of the illness; this patient slept with a pet dog.

INCUBATION PERIOD

It was impossible to determine the incubation period in any of our cases. Derrick¹ reported it to be fifteen days or less. In the outbreak of Q fever in a Chicago packing house, Shepard^{3d} expressed the belief that the incubation period was from nineteen to twenty-five days while a period of eleven to sixteen days was reported by another group^{3b}. In guinea pigs, the time between inoculation of the infective agent and the onset of illness varied between two and eighteen days.

ONSET OF ILLNESS

Our patients entered the hospital from two to seven days, with an average of four days, after the onset of symptoms. The onset of illness was considered to be acute in 7 cases and insidious in 5. In most other series the onset was considered to be acute, however, Feinstein, Yesner and Marks^{3c} reported an insidious onset in 70 per cent of 143 cases. Chills and fever, malaise, pain in the chest, headache, dizziness, vague aches and pains and anorexia were regarded in that order of frequency as the symptoms at the onset of the illness. Hornibrook and Nelson³ⁱ have reported two types of onset: one coryza-like, and the other associated with headache, chills and malaise. Diarrhea, photophobia, articular pain, nausea and vomiting were noticed by others as initial symptoms.

COURSE OF ILLNESS

Most of the patients entered the hospital at the beginning of the height of the disease and at entry had already had most of the symptoms that were observed during hospitalization. Nine of 12 patients had been seen by physicians before entrance, and 3 had received penicillin and a sulfonamide before entry. In all cases the objective physical signs were slight in comparison to the symptoms and the height of the fever.

Fever.—All our patients had fever before entrance into the hospital. The temperatures on admission ranged between 98.8 and 105 F with an average of 102.3 F. Five had initial temperatures above 104 and 9 above

102 F The temperature tended to remain high , multiple spikes occurred, probably owing to the effect of salicylate and antipyretic therapy The highest temperature recorded was 106 2 F , however, the temperature was above 105 F in 5 patients and above 104 F in 11 at some time during hospitalization In these 11 the temperature was above 104 F for an average of 4 5 days after admission, with a range of from two to seven days The duration of the fever was from four to twelve days, with an average of 7 8 days Subsidence of fever was by rapid lysis, only 2 patients had a definite crisis These observations are consistent with those of most other reports,¹⁷ although Derrick¹ observed several cases in which the fever was low grade and protracted In the 143 cases reported by Feinstein, Yesner and Marks,^{8c} 21 patients had no fever while in the hospital and the temperature was elevated above 102 F in less than half of the patients The duration of fever was observed by Irons and Hooper^{3f} to be from one to two weeks

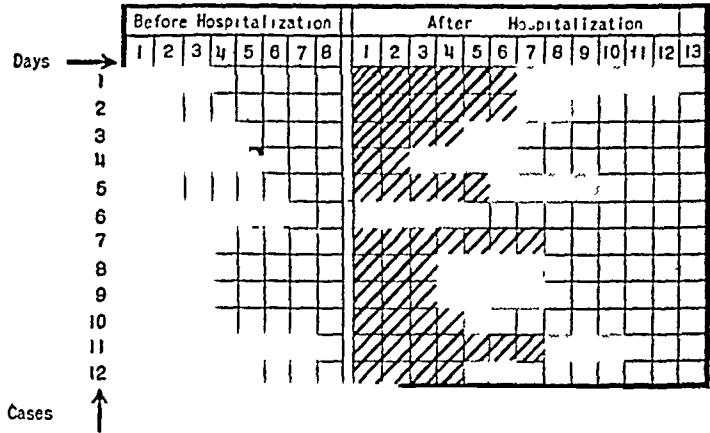


Chart 1—Duration of fever Cross-hatched blocks indicate temperature above 104 F , dotted blocks, temperature above 98 6 F

Pulse Rate—It is generally stated that patients with Q fever show a relative bradycardia early in the disease¹⁸ On entrance the pulse rate ranged between 70 and 124, with an average of 96 5, beats per minute in our cases One patient with a temperature of 104 F had a pulse rate of 70, while another with a temperature of 104 8 F had a pulse rate of 85 on admission However, other patients had pulse rates that were consistent with the elevation in temperature During hospitalization the pulse rate ranged between 70 and 100 and showed little relationship to the degree of fever It can therefore be stated that a relative bradycardia is consistent with the diagnosis of Q fever , however it is not essential in considering this disease

17 Foonote 3 a, b, d, f and i
18 Footnote 1 and footnote 3 a, b, c and i

Chills and Perspiration—Chills and profuse sweating were noted in 10 and 11 of our patients respectively. Sweating was usually of such a degree as to necessitate a change of bed linens. Chills were of moderate severity in most cases, however, occasionally they were frank rigor. These symptoms persisted during the duration of temperature above 102 F. Chills and profuse perspiration have been noted as common symptoms in all the reported series of cases.

Malaise and Weakness—Malaise and weakness were noted in all our patients and were regarded as the initial symptoms in 5. These were the most persistent complaints of our patients and were still present in 5 at the time of discharge. One patient suffered from excessive fatigue for as long as three months after the onset of his illness. Generalized muscular

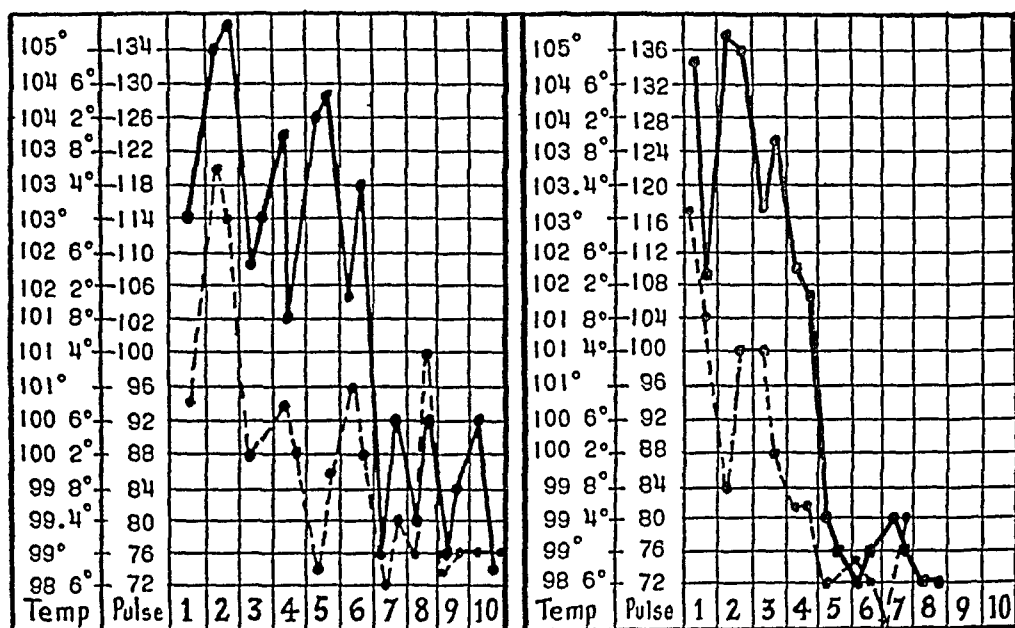


Chart 2—Graphic representation of temperature (solid line) and pulse rate (dotted line)

aches and pains were noted in six cases. These observations are consistent with the experience of others.

Respiratory System—In 9 of our 12 patients, pneumonitis was demonstrated on roentgenologic examination. Of the 3 without pneumonitis, 1 complained of severe pain in the chest, and this symptom persisted for three days. The other 2 patients had no symptoms referable to the respiratory tract. Of the 9 patients with pulmonary involvement, 5 complained of thoracic pain at some time during the illness. This pain was usually of moderate severity and of short duration. The respiratory rate was essentially normal with slight transient elevation. In 1 patient with pneumonitis, there was a transient increase in the respiratory rate to 45 per minute. Eight patients had a cough, usually dry. Slight expectoration was present in 4, and hemoptysis was present in 3. Despite

the presence of pneumonitis, the respiratory symptoms and signs were not conspicuous. In one reported series of cases,³¹ more than half of 15 patients with pneumonitis complained of vague thoracic pain in the sub-sternal region that was not related to respiration. Shepard^{3d} and Robbins and Ragan^{3a} noted pain in the chest in half of their patients and stated that this was rarely a true pleuritic pain but was rather of a neuralgic character. In another series,^{3c} pleuritic pain was present in 35 per cent of 143 cases. In other reports expectoration was minimal and blood tinged-sputum infrequent. Derrick¹ did not include the presence of pneumonitis as part of the syndrome, but in all subsequent epidemics of Q fever, pulmonary involvement was mentioned in the majority of cases.

Gastrointestinal System—All our patients complained of anorexia, and 8 had nausea and vomiting. These symptoms usually persisted for one or two days, however, in 1 case vomiting lasted for eight days even though only small amounts of fluid were given orally. This patient also experienced postcibal vomiting twenty-five days after admission, and this persisted until the time of discharge, eight days later. Nausea and vomiting were recorded frequently by other investigators.¹⁹ Abdominal pain was prominent in 2 cases. This was vague and referred to the epigastrium and right upper quadrant. Diarrhea of one day's duration was present in 1 case, constipation was not recorded in any case. Derrick¹ reported constipation as being a prominent feature of the disease, and it was also present in 33.6 per cent of 143 patients in a series reported by another author. Robbins and Ragan^{3a} observed a few patients with gastrointestinal complaints, including diarrhea.

Headache—Headache was reported as the outstanding symptom of Q fever by many authors.²⁰ It was described as severe and persistent. Robbins and Ragan^{3a} described the headache as mainly frontal with retro-orbital pain on movement of the eyeballs, while nuchal pain was most frequent in other instances.⁵ Shepard^{3d} stated that none of 33 patients mentioned headache until directly questioned and even then most said that they had not had this symptom. As stated previously, 2 patients experienced headache as the initial symptom, and 11 patients suffered from it at some time during their illness. Headache was severe and persistent, lasting an average of six days, with the longest duration fourteen days. The headache was frontal in those cases in which the location was recorded. Codeine was often necessary for relief.

Neurologic Findings—Two of 11 patients complained of dizziness, while 1 had this as the initial feature of his disease. Stupor and confusion were noted in 2 cases, restlessness and insomnia were commonly

19 Footnote 1 and footnote 3 a, c, d and i

20 Footnote 1 and footnote 3 a, b and i

observed during the acute stage of the disease Derrick¹ observed drowsiness and stupor in his most severely ill patients and classified these patients as showing the typhoidal type of the disease These observations were consistent with those in other reported cases

Miscellaneous Symptoms—Epistaxis was noted in 1 case, but it was not severe and was of short duration Frequency and burning on urination were observed in 1 case We have the impression that most of our patients lost some weight during hospitalization, but the weight loss was recorded in only 1 case, in this case it was 22 pounds (10 Kg) Photophobia was present in 2 cases All these symptoms, except frequency and burning on urination, were mentioned infrequently in other reports However, Derrick¹ observed photophobia as a common symptom in his cases

	Number of Cases →											
	1	2	3	4	5	6	7	8	9	10	11	12
Malaise and Weakness												
Headache												
Anorexia												
Nausea and Vomiting												
Cough												
Expectoration												
Hemoptysis												
Muscular Aches and Pains												
Chest Pain												
Dyspnea												
Chills												
Profuse Sweating												
Epistaxis												
Dizziness												
Photophobia												
Abdominal Pain												
Stupor and Confusion												

Chart 3—Incidence of symptoms

Physical Findings—The significant observations on physical examination in Q fever are usually scant Six of our 12 patients appeared in acute distress on admission Four appeared moderately ill, and 2 seemed to be well Four of the patients were described as having flushed facies Three had a light yellow-coated tongue A slightly injected pharynx was observed in 8 patients, a condition which was described in other series^{3a, c} The conjunctivas were congested in 2 patients Stiffness of the neck was seen in 3 of 15 cases by Hornibrook and Nelson³¹ and was also observed by Robbins and Ragan^{3a} Moderate nuchal spasm was observed in 2 of our patients Lymph nodes were palpable in 5 of our patients, however, this condition was rarely recorded in other reports Splenomegaly and hepatomegaly were not observed in any of our patients and have been found to be rare in Q fever A cutaneous rash was present in 4 of our patients at some time during the illness It was

present in only 1 patient on admission and was described as a fine confluent red rash involving the face, chest, shoulders and back. It faded rapidly in two days. The remaining 3 patients had been given penicillin, and in 2 of them the skin manifestations were probably a sensitivity reaction to the antibiotic. A typical rash is unusual in Q fever, but Derrick¹ described its presence in 1 of 7 patients. Physical findings on examination of the chest were usually slight. They were completely absent in 2 patients with pneumonitis. In 7 patients with pneumonitis there were fine crepitant rales, in 5, bronchial breath sounds, in 2, increased vocal fremitus, and in 1, impaired resonance and respiratory lag. These conditions persisted for four to six days after admission, however, in 1 patient thoracic abnormalities persisted until the eighteenth day. Signs when present were always over the area of pulmonary involvement. Hornibrook and Nelson²¹ reported absence of thoracic abnormalities in 15 cases of pneumonitis. Fine rales were observed in most reported cases²¹. In another series a friction rub was found in 5 of 15 patients with pneumonitis. In most patients these findings were transient. Derrick¹ did not consider pneumonitis as part of the disease in his original report. An apical systolic murmur was recorded in 2 cases. Abdominal tenderness with moderate distention and costo-vertebral tenderness were found in 1 each of our patients. Derrick¹ reported the presence of jaundice in 1 patient.

Convalescence—Convalescence was usually rapid after patients were admitted to the hospital. They became relatively asymptomatic from six to fifteen days after admission, with an average of 10.9 days. However, residual weakness and fatigue persisted in 5 patients, in 1 lasting for three months after discharge from the hospital. One patient complained of postcibal nausea and occasional vomiting of about one month's duration after discharge. The average duration of hospitalization was 19.2 days. One patient recently returned to the hospital, nine months after onset of illness, complaining of fever, malaise and muscular pains, the complement fixation test for Q fever elicited a positive reaction in a titer of 1:64, and his temperature on admission was 100 F, no other cause for his illness could be ascertained. Robbins and Ragan²² reported a protracted course in severe cases and an average hospitalization of twenty-two days. Feinstein, Yesner and Marks²³ observed an average duration of illness of four days. Derrick¹ stated that convalescence was variable and recovery was not complete in some cases for as long as five months. Arthritis, orchitis and epididymitis were observed as late complications in one series,⁵ and ascites, jaundice, pedal edema and heart failure were reported in cases from Australia.

21 Footnote 3 a, b and c

LABORATORY OBSERVATIONS

Blood—Several blood counts were done in all our cases. The red blood cell count was never above 5,000,000 on entry, and in only 2 did it reach that figure at any time during hospitalization. Five patients had a count below 4,000,000 on one occasion each, usually about four days after admission. One patient had 2,040,000 red blood cells per cubic millimeter on admission, but the count rapidly became normal without specific therapy. The white blood cell count varied between 3,600 and 14,200. Seven patients had a white cell count below 6,000 on at least one occasion, and only 5 had an elevation of the white blood cells above 10,000 during hospitalization. A differential count showed the neutrophils above 70 per cent in all cases on entry, while the lymphocytes were below 25 per cent. There was an increase in the percentage of lymphocytes in all patients, and on recovery the number of these cells usually

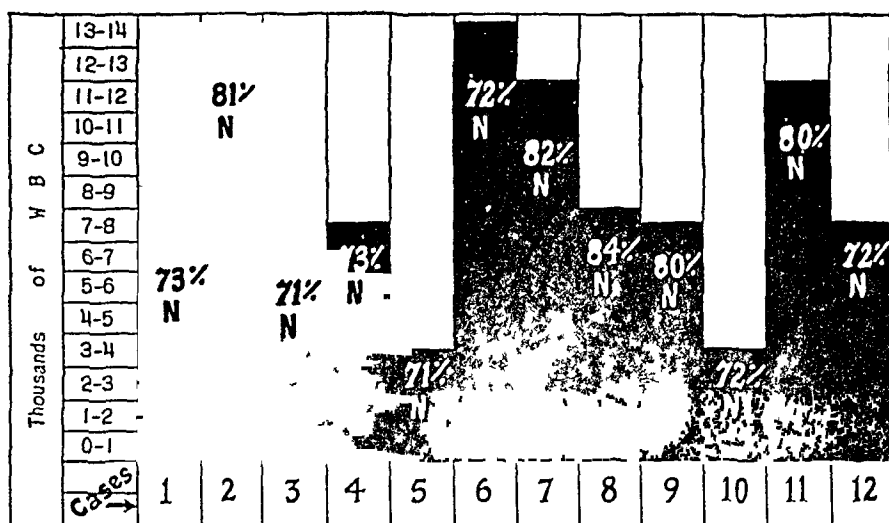


Chart 4—Initial leukocyte counts

approximated that of the neutrophils. The sedimentation rate was elevated in all patients and was above 25 mm per hour in 9. These observations are consistent with those reported by other authors.²²

Urine—Albuminuria, 1 or 2 plus, occurred in 8 patients and disappeared when the temperature subsided. A few cellular elements and casts were found in most instances. Occasional albuminuria has been reported in all other series.

Roentgenograms of the Chest—The pneumonitis of Q fever presents a variable roentgenologic picture. A patchy infiltration was present in 6 of our patients, a diffuse homogeneous density in 2 and a fine confluent infiltration in 1. Any one or several lobes may be involved in the process. In our patients the middle and lower lobes of the right lung

²² Footnote 1, footnote 3 a, b, and c, footnote 5

were involved in 3, the lower and middle lobes of the right lung, in 2, the upper lobe of the right and of the left lung in 1, and the upper lobe of the right lung, the upper lobe of the left lung and the lower lobe of the left lung separately, in 1 case each. On repeat roentgenograms made four to eight days after admission, an increase in the extent of involvement was noted in 7 cases. Regression of the pulmonic infiltration occurred,

TABLE 1—*Roentgen Changes Observed in Patients with Pneumonitis*

Case	Day															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	+				I											C
2	+			I				I					O			
3	+												O			
4	+					S						C				
5	+		I			I							C			
6	+															
7	+				I				C							
8	+				I											O
9	+		I				I			O				O		

Explanation of symbols: +, infiltration present; I, increased; S, no change; C, clearing. In case 6 roentgenograms were not repeated.

TABLE 2—*Results of Laboratory Studies*

Procedure	Day											
	1	2	3	4	5	6	7	8	9	10	11	12
Roentgenograms	+	+	+	+	+	+	+	—	—	—	+	+
Blood cultures	—	—	—	—	—	—	—	—	—	—	—	—
Serologic tests	—	—	—	—	—	—	—	—	—	—	—	—
Spinal tap	—	—	—	—	—	—	—	—	—	—	—	—
Sputum examination	—	+	*	—	+	+	—	—	—	—	—	—
Electrocardiogram	—	—	—	—	—	—	—	—	—	+	—	—
Urinalysis (albumin)	+	+	+	—	+	+	—	+	+	+	+	+
Liver function tests	+	—	—	—	—	—	—	—	—	—	—	—
Malarial smears	—	—	—	—	—	—	—	—	—	—	—	—
Cold agglutination	—	—	—	—	—	—	—	—	—	—	—	—
Heterophile agglutination	—	—	—	—	—	—	—	—	—	—	—	—
Agglutination for Brucella A	—	—	—	—	—	—	—	—	—	—	—	—
Agglutination for typhoid A	—	—	—	—	—	—	—	—	—	—	—	—
Agglutination for paratyphoid A	—	—	—	—	—	—	—	—	—	—	—	—
Agglutination for tularemia	—	—	—	—	—	—	—	—	—	—	—	—
Weil-Felix test	—	—	—	—	—	—	—	—	—	—	—	—

* *Aspergillus* cultured

† *K. pneumoniae* type B cultured

‡ Left axis deviation shown

usually by the twelfth to the sixteenth day. However, in no case did the roentgenogram of the chest taken at the time of discharge show completely normal conditions. One patient was followed with chest roentgenograms at regular intervals for three months after discharge, and residual increased vascular markings were noted during that entire period. The roentgen findings were interpreted as being consistent with an

atypical pneumonia in 7 cases and as a pneumonic consolidation in 2 cases. Robbins and Ragan^{3a} reported pulmonary involvement in 190 of 266 cases. They stated that the lower lobes were more frequently involved and that a minimal effusion was noted in 4 of 51 cases. Our observations and the persistence of the pneumonic process are consistent with other reports, but Feinstein, Yesner and Marks^{3c} stated that in 102 of 147 cases of pneumonic involvement, the roentgenogram of the chest revealed normal conditions after an average of 10.8 days.

Other Laboratory Studies—Spinal puncture with examination of fluid was done in the 2 cases with nuchal rigidity. Dynamics and chemical constituents were normal and culture negative. In the infrequent reports of this examination in other series the results of spinal fluid examination have been negative³¹. Studies of sputum in 8 cases showed the usual flora in 6, minimal growth of *Aspergillus* in 1 and *Klebsiella pneumoniae* type B in 1. Results of hepatic function tests done in 3 cases were normal in 2, 1 patient had an icteric index of 10.8 and increased urobilinogen in the urine on three examinations. Electrocardiograms were made in 6 cases, 5 showed no abnormalities, and 1 showed left axis deviation. Routine and cold agglutination tests, Wassermann tests, heterophile agglutination tests, Weil-Felix tests, smears for malaria and blood cultures were done in the majority of our cases, and results were reported as negative.

DIAGNOSIS

The diagnosis of Q fever depends on the demonstration of a positive reaction following a negative one or a significant rise, fourfold or greater, in the complement fixation titer of the patient's serum. Blood for this determination should be drawn as soon as possible, preferably before the ninth day of illness and again fourteen to twenty-one days later. Agglutination tests for Q fever were first described by Burnet and Freeman⁸ at the time of the discovery of this disease. The complement fixation reaction becomes positive usually after the ninth day of illness. However, in 1941 Bengtson²³ reported that in the complement fixation test the antibodies were present in human serum thirteen days after the onset of the fever. The titer of the serum increased in twenty-two to twenty-three days and she found a titer of 1:32 in 2 of 13 cases on the three hundred and eighty-fifth and three hundred and fifth day respectively after onset. A rise in titer in the complement fixation test, however mild the disease, is regarded as definite evidence of Q fever. The diagnoses in our cases, as in all other reports, were made by this serologic test. However, in some epidemics²⁴ demonstration of the rickett-

23 Bengtson, J. A. Complement Fixation in Q Fever, *Proc. Soc. Exper. Biol. & Med.* **46**: 665-668, 1941.

24 Smadel, J. J., Snyder, M. J., and Robbins, F. C. Vaccination Against Q Fever, *Am. J. Hyg.* **47**: 71-81, 1948. Burnet and Freeman⁸.

sial organism by inoculation of guinea pigs confirmed the diagnoses. The Weil-Felix reaction was negative in our cases, as in other reported series²⁵

The admitting diagnoses were atypical pneumonia in 6 cases, atypical pneumonia, probably Q fever, in 1 case, fever, origin undetermined, in 2 cases, influenza in 2 cases, and lobar pneumonia in 1 case. Q fever was listed as a disease to be ruled out in 3 other patients. Infectious mononucleosis, malaria, pyelitis, infectious hepatitis, brucellosis, poliomyelitis, meningitis and rheumatic fever were listed as possibilities in various cases. These diseases were also considered initially in other reports^{3a, d}. Grip, infection of the upper respiratory tract, bronchitis, gastroenteritis and tuberculosis were initial diagnoses in other series^{3d}.

One patient showed a definite psychotic reaction for three days during the height of the illness. This case will be reported elsewhere.

INCIDENCE

Since September 1947 all patients admitted to the Medical Service of Birmingham Veterans Administration Hospital with an influenzal syndrome, atypical pneumonia or fever of undetermined origin were tested routinely for Q fever complement fixation immediately after admission and fourteen days or longer after the first test. The tests were performed at the Hondo Q Fever Laboratory of the United States Public Health Service, at Hondo, Calif., and since early 1948 in duplicate by our own laboratory and the laboratory at Hondo. We tested 93 patients with these diagnoses between Sept. 4, 1947 and July 31, 1948, when the compilation of this report was terminated. Among these 93 there were 20 with positive agglutination reactions for Q fever (21.5 per cent), hence it is obvious that the incidence of Q fever among patients seriously enough ill to be hospitalized with illness simulating influenzal syndrome, atypical pneumonia or fever of undetermined origin during this period of approximately eleven months was astoundingly high. From Aug. 1, 1948 to June 15, 1949, a similar period of approximately eleven months, we performed agglutination tests for Q fever on the serums of 201 patients with similar diagnoses and have obtained positive results in only 6 cases (2.98 per cent). Even admitted that the per cent difference in incidence of this disease during these two like periods was influenced possibly by the greater number of patients tested during the latter eleven month period, we feel that the difference in the numbers of patients with diagnoses of Q fever during these two periods is significant. Other

25 Irons, J. V., Murphy, J. N., Jr., and Wolfe, D. M. Q Fever in the United States. Serological Observations in an Outbreak Among Stock Handlers and Slaughterhouse Workers, *J. A. M. A.* **133** 819-820 (March 22) 1947.

reports of this disease in the literature refer to its as occurring in epidemics, but the groups of diseased persons described were compact and had similar exposure to the infective agent. Our patients came from widely separated areas in Los Angeles County. These facts tend to support a conclusion that Q fever may occur in epidemic form during certain periods and surely the incidence is so high during such periods that it commands attention among communicable diseases of epidemiologic interest.

MORTALITY

The mortality rate of Q fever is less than 1 per cent. We had no deaths from this disease at this hospital. Hornibrook and Nelson³¹ reported 1 death among 15 patients. Two brothers died of Q fever during the Texas epidemic in 1946. There have probably been two deaths from Q fever in Los Angeles County. The gross observations at autopsy in 1 of these cases have been published.¹⁵

With the increase in the incidence of Q fever, methods of prophylaxis in persons with possible exposure by reason of occupation have been studied. In one report of a laboratory outbreak³² it was found that Rocky Mountain fever vaccine may give some protection against Q fever. Guinea pigs showed a definite resistance to the infection after vaccination, the duration of fever was shorter, and the mortality rate was decreased from 40 to 80 per cent to 2 per cent. In 28 vaccinated human patients complement-fixing antibodies were present in a significant titer.

TREATMENT

The management of Q fever at this hospital was similar to that reported in other places. Supportive therapy, which included forcing of fluids and use of analgesics, was administered in all cases. Intravenous administration of fluids was considered to be necessary in 6 cases, being given for an average of five days, with a duration of sixteen days in 1 case. Antispasmodics for the control of abdominal cramps were administered to 3 patients. Four of our patients received both sulfonamides and penicillin, 3 received sulfonamides alone, 3 received penicillin alone, and 2 received no chemotherapy or antibiotic therapy. When penicillin and sulfonamide drugs were given, they were administered for an average of 6.6 and 4.3 days respectively. No significant beneficial results were observed with these drugs. Our observations are consistent with results as reported by other workers.²⁶ Paraaminobenzoic acid, because of its beneficial effect in other rickettsial diseases, has been tried and has proved of little or no value. Experimentally, streptomycin has been observed to exercise a rickettsiostatic action on the growth of *R. burnetii* in the yolk sacs of fertile eggs and to lower the

26 Footnote 3 a, c and 1

mortality rate in guinea pigs inoculated with highly virulent suspensions of *R. burneti* ²⁷ In a reported case of Q fever treated with streptomycin, clinical improvement was attributed as possibly due to the use of this drug ²⁸ A new antibiotic, aureomycin hydrochloride, has been shown to display exceptional curative powers in experimental Q fever in animals It has been used in several cases of human Q fever and has been noted to exert a beneficial effect in some cases However, it is not possible at present to evaluate conclusively the role of this drug in the therapy of Q fever Aureomycin to be effective has to be employed early in the disease, prior to the time that the diagnosis can be established by serologic study Hence, it has to be used empirically However, even in those cases in which the drug is effective in controlling or aborting the disease, it does not interfere with antibody formation, therefore a positive serologic diagnosis may be made even if the patient has become asymptomatic

In conclusion, it may be stated that Q fever is a protean disease, acute in character but with a variable course with widespread distribution throughout the U S and probably the world It is probably caused by a rickettsial organism Dairy farm and other animals probably served as a reservoir for the infection and transmission is probably an air-borne mechanism It presents no definite distinguishable clinical features, and diagnosis depends on a high index of suspicion in any epidemic of acute illness and on a positive serologic reaction The utilization of prophylaxis and specific therapy will probably be of benefit, however, these measures are still in the investigative stage

SUMMARY

A brief review of the literature concerning Q fever is presented

Twelve cases of Q fever with positive serologic study are summarized

Clinical features of Q fever as observed in these cases are presented and compared to the reports from the literature of other cases of Q fever

Therapy for this disease is discussed briefly

The incidence of Q fever was 21.5 per cent in a group of hospitalized veterans admitted with the diagnosis of influenzal syndrome, atypical pneumonia or fever of undetermined origin during an eleven month period (1947-1948) In a similar eleven month period (1948-1949) the incidence was 2.98 per cent in patients admitted with similar diagnoses

²⁷ Huebner, R. J., Hottle, G. A., and Robinson, E. B. Action of Streptomycin in Experimental Infection with Q Fever, *Pub. Health Rep.* **63** 357-362, 1948

²⁸ Rosove, L., West, H. E., and Bower, A. G. Q Fever Case Treated with Streptomycin, *Am. Int. Med.* **28** 1187-1193, 1948

PATHOLOGY OF SUBCHRONIC ATROPHY OF THE LIVER

Comparison with Laennec's Cirrhosis

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AND

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DETAILS have already been published of a considerable number of fatal cases of chronic hepatitis¹ in Denmark during the years 1944 to 1947. The pathoanatomic picture corresponded to what was described in earlier literature as subchronic atrophy of the liver,² synonyms for which were subacute diffuse necrosis of the liver, subacute yellow atrophy of the liver, toxic cirrhosis and necrotic hepatitis.

The aim of this work is to give a detailed description of the pathologic changes in the liver in this rare disease on the basis of data obtained from considerable postmortem material.

We found it of interest to make a comparison with the cases of Laennec's cirrhosis in which autopsies were made during the same period, since subchronic atrophy of the liver offers clinically a number of points of similarity with Laennec's cirrhosis.

As a few biopsies of the liver were made, we endeavored to solve the problem of whether it is possible with the aid of biopsy at an early stage of the disease to distinguish subacute atrophy of the liver from acute hepatitis and from cirrhosis of the liver.

This study was supported by a grant from the King Christian X Fund.

From the Pathological Institute (Dr S. Petri, Director and Chief Anatomist) and the Third Medical Department (Dr Poul Iversen, Physician in charge), Kommunehospitalet.

1 (a) Bjørneboe, M., and Brøchner-Mortensen, K. Prognosis in Acute Hepatitis, *Ugeskr. f. Læger* **107** 715-718, 1945. (b) Jersild, M. Increasing Frequency of Chronic Hepatitis, *ibid* **107** 819-822, 1945. Infectious Hepatitis with Subacute Atrophy of the Liver, *New England J. Med.* **237** 8-13, 1947. (c) Alsted, G. Studies on Malignant Hepatitis, *Am. J. M. Sc.* **213** 257-267, 1947. (d) Bjørneboe, M., Jersild, M., Lundbæk, K., Hess-Thaysen, E., and Ryssing, E. Incidence of Chronic Hepatitis in Women in Copenhagen, 1944-45, *Lancet* **1** 867-868, 1948.

2 Bergstrand, H. Ueber die akute und chronische gelbe Leberatrophy mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, Leipzig, Georg Thieme, 1930.

Finally, on the basis of both groups of material, we tried to discover whether there is a connection between the size of the liver at autopsy and the occurrence of various symptoms, especially that of hepatic insufficiency

Only scanty reports concerning the pathology of subchronic atrophy of the liver have been published. In Bright's work,³ a typical case of the disease was described, but Marchand⁴ was the first to recognize its relation to acute atrophy of the liver. Wilson and Goodpasture⁵ described a single case and referred to older publications dealing with the subject.⁶ Bergstrand² discussed, in his work on acute and chronic atrophy of the liver, 150 cases of these diseases. Eleven of them in which there were symptoms of the disease over a period of three months were presumably of the same nature as those described in this report. In the years following, a few similar cases were described. Lucke⁷ reported in 1944 that among 125 fatal cases of hepatitis there were 7 of more than three months' duration from the first symptom until death.

In a condition of subchronic atrophy, the liver is as a rule greatly and uniformly reduced in size (fig 1). The surface is smooth or wrinkled, and in cases of longer standing it is nodular. It is yellow and red. In the yellow parts the surface is domed, and in the red parts it is depressed. On the surface of the section, yellow "islands" are to be seen, separated by the red, depressed parts. Under the microscope it is found that the liver parenchyma has completely disappeared in the red parts, where there are only vessels and connective tissue infiltrated with inflammatory cells with some "proliferation of the bile ducts." The yellow "islands" consist of cells of the liver parenchyma, to some extent with degenerative and necrotic changes. The trabecular structure is indistinct.

3 Bright, R. Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy, London, Longman [and others], 1828, p. 105, plate 6.

4 Marchand, F. Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasie, Beitr. z. path. Anat. u. z. allg. Path. **17**: 206-219, 1895.

5 Wilson, J. D., and Goodpasture, E. W. Yellow Atrophy of the Liver. Acute, Subacute and Healed, Arch. Int. Med. **40**: 377-385 (Sept. 27) 1927.

6 MacDonald, S., and Milne, S. L. Subacute Liver Atrophy, J. Path. & Bact. **13**: 161-173, 1909. Mallory, F. B. Cirrhosis of the Liver. Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**: 69-75, 1911. Miller, J., and Rutherford, A. Liver Atrophy, Quart. J. Med. **17**: 81-100, 1923. Pratt, J. H., and Stengel, A. Toxic Cirrhosis Resulting from Acute Liver Atrophy, Tr. A. Am. Physicians. **41**: 100-110, 1926. Strauss, H. Ueber subacute Leberatrophie mit Aszites und dessen Beziehungen zur Leberzirrhose, Deutsche med. Wchnschr. **46**: 487-488, 1920.

7 Lucke, B. The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**: 471-527, 1944.

MATERIAL

Subchronic Atrophy of the Liver—The material consisted of 108 cases in which autopsies were performed at the pathologic institute of Kommunehospitalet during the period from Jan 1, 1944 to Jan 1, 1948. Only 6 subjects were men, whereas 102 were women. This considerable preponderance of women, which was shown by Ryssing⁸ to exist in a previous study, could not be explained. The age range of the dead subjects is shown in figure 2. It can be seen that the curve in the case of



Fig 1—Cut surface of the liver of a woman of 71 with subchronic atrophy of the liver of five weeks' duration

women rises steeply after the forty-fifth year, a circumstance which could not be explained.

With regard to the distribution of the material within the period from 1944 to 1948, it must be noted that autopsies were performed in 78 of the 108 cases between June 1945 and October 1946.

There are included in this group all cases in which the macroscopic picture corresponded to that of subchronic atrophy of the liver. In very

⁸ Ryssing, E. Hepatitis in Copenhagen, *Ugeskr f læger* **110** 1099-1102 1948

few cases the diagnosis was in some doubt, as forms were noted which were in a state of transition toward Laennec's cirrhosis. In 1 instance chronic atrophy was even seen in one lobe of the liver and Laennec's cirrhosis in the other. By far the greater part of the material showed, however, a typical and uniform appearance.

Laennec's Cirrhosis—This material consisted of all cases of Laennec's cirrhosis (portal cirrhosis) in which autopsies were made at Kommunehospitalet in the period from January 1944 to January 1948, or

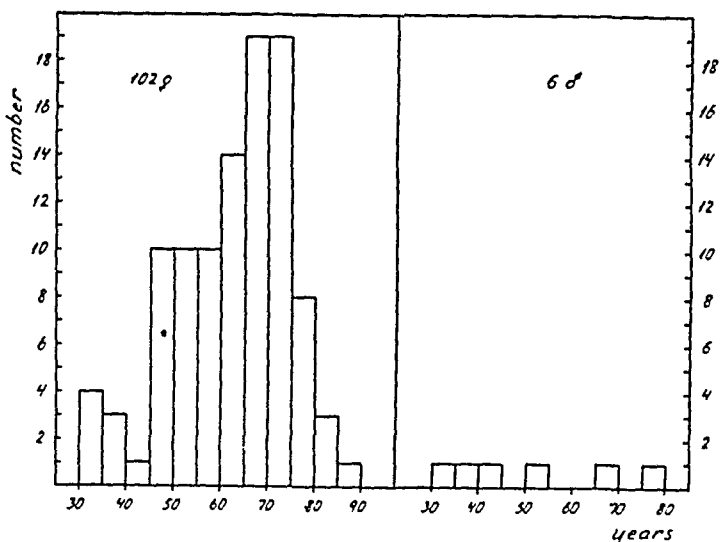


Fig 2—Age and sex distribution in subchronic atrophy of the liver

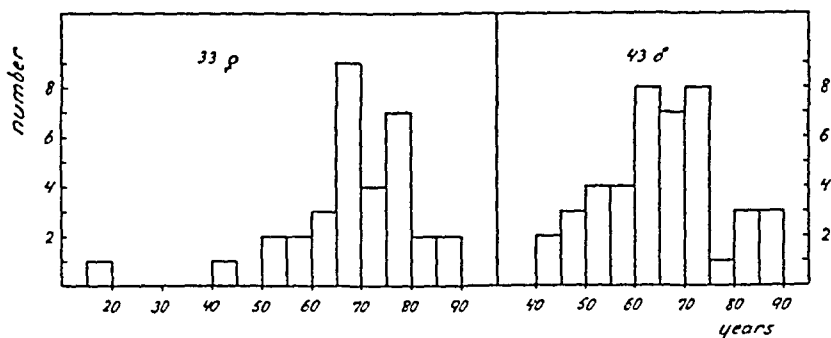


Fig 3—Age and sex distribution in Laennec's cirrhosis

76 cases in all (cases of biliary cirrhosis or chronic stasis of the liver were excluded). Thirty-three subjects were women and 43 men, a distribution between the sexes essentially different from that in subchronic atrophy of the liver. The age range is shown in figure 3, which indicates that the maximum incidence fell within the age group of 60 to 80. No definite difference was seen between the distributions for men and women, nor did there appear to be any definite distinction in the age ranges in subchronic atrophy of the liver and in Laennec's cirrhosis.

On examination of the postmortem records from 1928 to 1947 inclusive (fig 4), it was clearly seen that the number of cases of Laennec's cirrhosis had been relatively constant over those years (about 20 per year in 900 to 1,000 autopsies), whereas the number of cases of subchronic atrophy of the liver showed an enormous increase beginning in 1944, formerly, this type had appeared only sporadically. With regard to the distribution between the sexes, it can be seen that, whereas Laennec's cirrhosis had formerly occurred mainly in men (fig 4), in the years 1944, 1945 and 1946 a relatively larger number of cases were recorded among women. We shall deal with this situation in more detail later in this report.

PATHOLOGIC ANATOMY

Macroscopic Anatomy—Weight of the Liver In 28 autopsies in cases of subchronic atrophy of the liver chosen at random (25.9 per cent

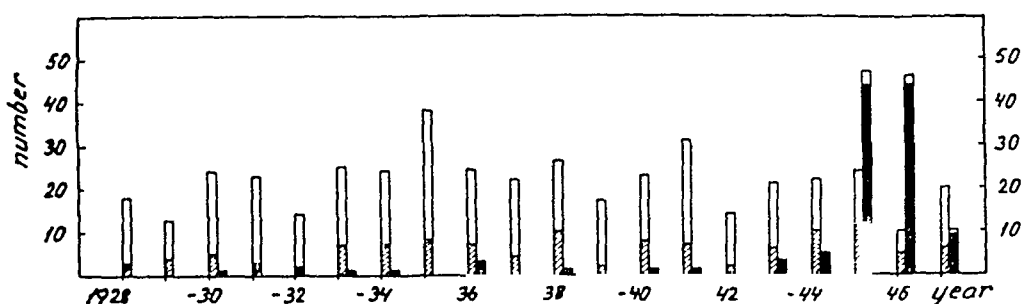


Fig 4—Occurrence of subchronic atrophy of the liver (columns on the right) and Laennec's cirrhosis (columns on the left) in postmortem material of Kommune-hospitalet in the years 1928 to 1947. Shaded areas indicate female patients.

of the total cases of this condition), the weight of the liver was measured. In 7 instances it weighed less than 700 Gm, in 14 between 700 and 900 Gm and in 7 over 900 Gm. In other words, there was a pronounced reduction of the liver parenchyma (the normal weight is 1,450 to 1,750 Gm⁹).

Size of the Liver In all autopsies, the measurements of the liver were given in the three planes. We multiplied these three figures together to form an estimate of the volume of the liver, knowing full well that that value could be at most only an approximate figure for the cubic content (hereinafter called the volume index). In figure 5 is shown the relation between the weight of the liver and the volume index in the 28 cases mentioned previously, a close correlation was

⁹ Tumen, H. J. Anatomy and Physiology of the Liver, in Bockus, H. L., and others. Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1946, vol. 3, p. 1.

noticed, and for that reason we later felt ourselves at liberty to use the volume index as a measurement for the size of the liver

In figure 6 is the distribution according to the volume index for 104 cases of subchronic atrophy of the liver and 73 cases of Laennec's cirrhosis. Subchronic atrophy of the liver entails, as a whole, a con-

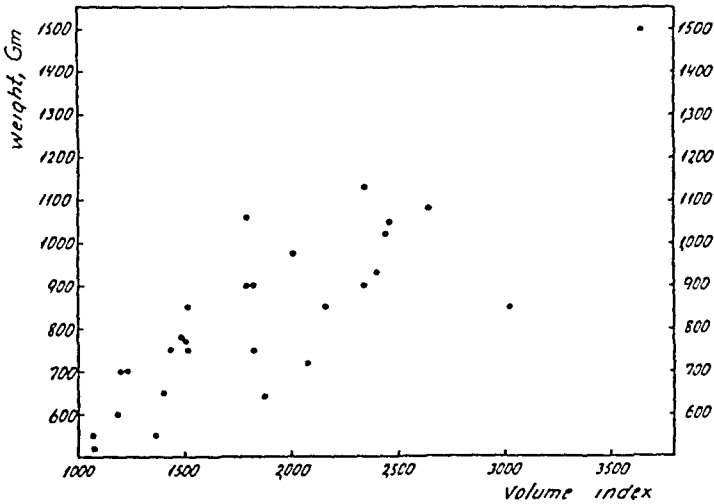


Fig 5—Relation between weight and volume index of the liver in 28 cases of subchronic atrophy of the liver

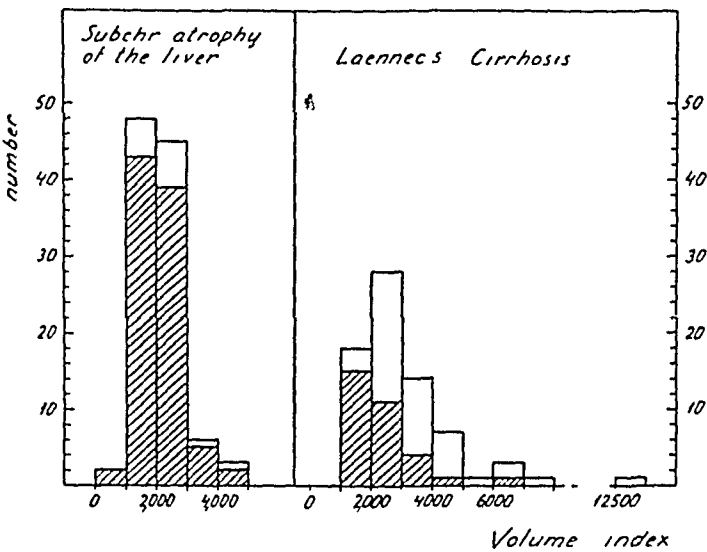


Fig 6—Volume index of the liver for 104 cases of subchronic atrophy of the liver and 73 cases of Laennec's cirrhosis. The shaded areas indicate death from hepatic coma

siderably greater reduction of the liver than Laennec's cirrhosis. In 48 per cent of the cases of subchronic atrophy of the liver there was a volume index below 2,000, whereas in only 25 per cent of those of Laennec's cirrhosis was there a volume index below the figure

Carcinoma of the Liver Five instances of primary carcinoma of the liver (6.6 per cent of the total) and 4 of hepatomas were observed among the subjects with Laennec's cirrhosis, whereas neither disorder was observed among 108 with subchronic atrophy of the liver. Berk and Lieber¹⁰ observed primary carcinoma in 4.5 per cent of the subjects with cirrhosis of the liver, whereas 67 per cent of those with primary carcinoma of the liver also had cirrhosis of the liver.

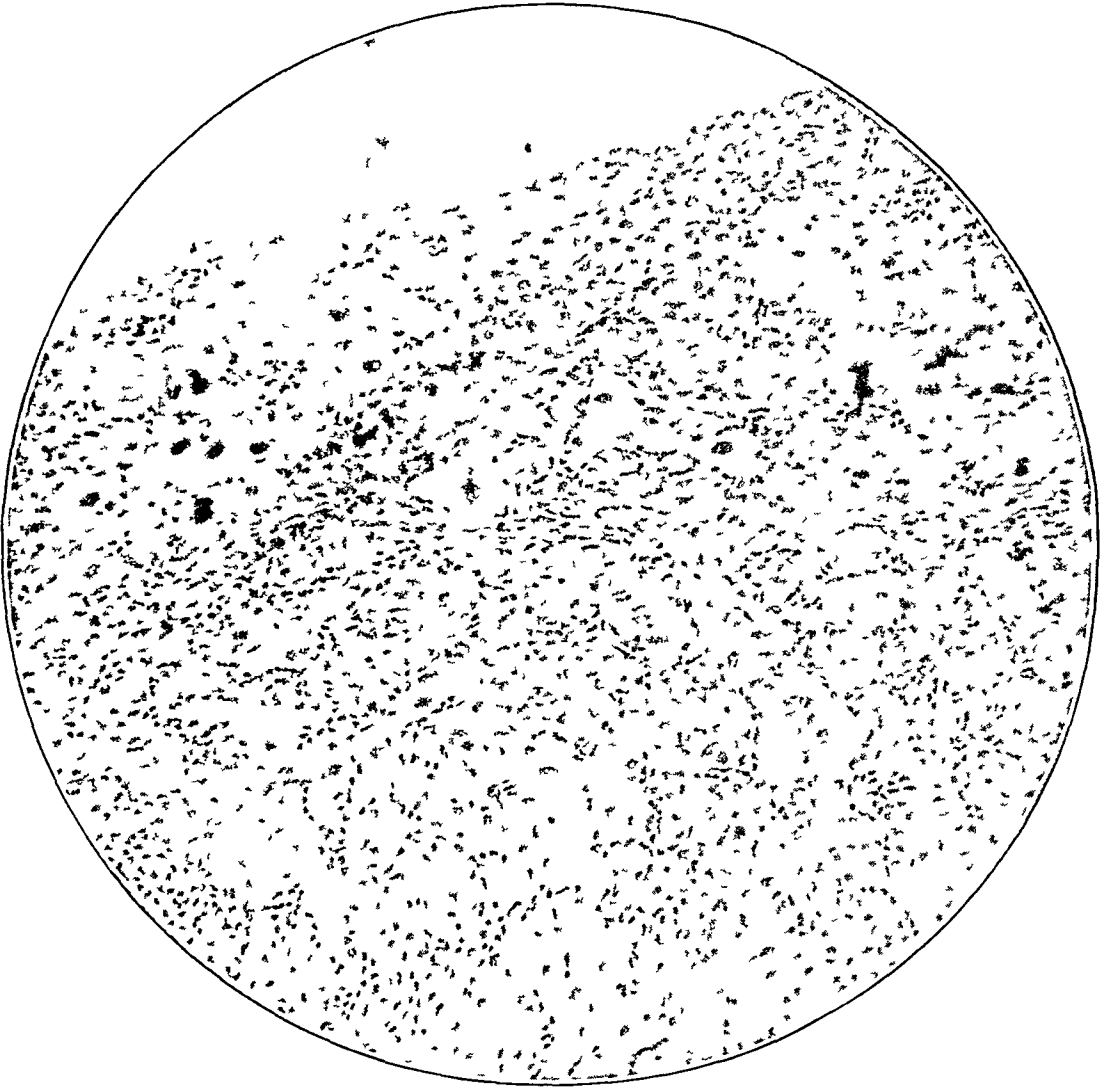


Fig 7—Biopsy specimen of the liver of a woman of 56 with subchronic atrophy of the liver, taken after two months' duration of symptoms. The duration of the disease to death was four and one-half months.

Cholelithiasis Among the subjects with Laennec's cirrhosis there were 21 (28 per cent) with gallstones (2 of these had undergone cholecystectomy directly before death), whereas 20 (18.5 per cent) of the subjects with subchronic yellow atrophy of the liver had gallstones.

¹⁰ Berk, J. E., and Lieber, M. M. Primary Carcinoma of the Liver in Hemochromatosis, *Am J M Sc* **202** 708-714, 1941.

In all instances in subchronic atrophy of the liver this disorder is a matter of small pigment stones, presumably formed during the course of the disease¹¹ The cases in which the diagnosis was assumed beforehand to be biliary cirrhosis were not included in the material The figures were scarcely higher than could be expected according to the age range and the sex distribution of the types of material¹²

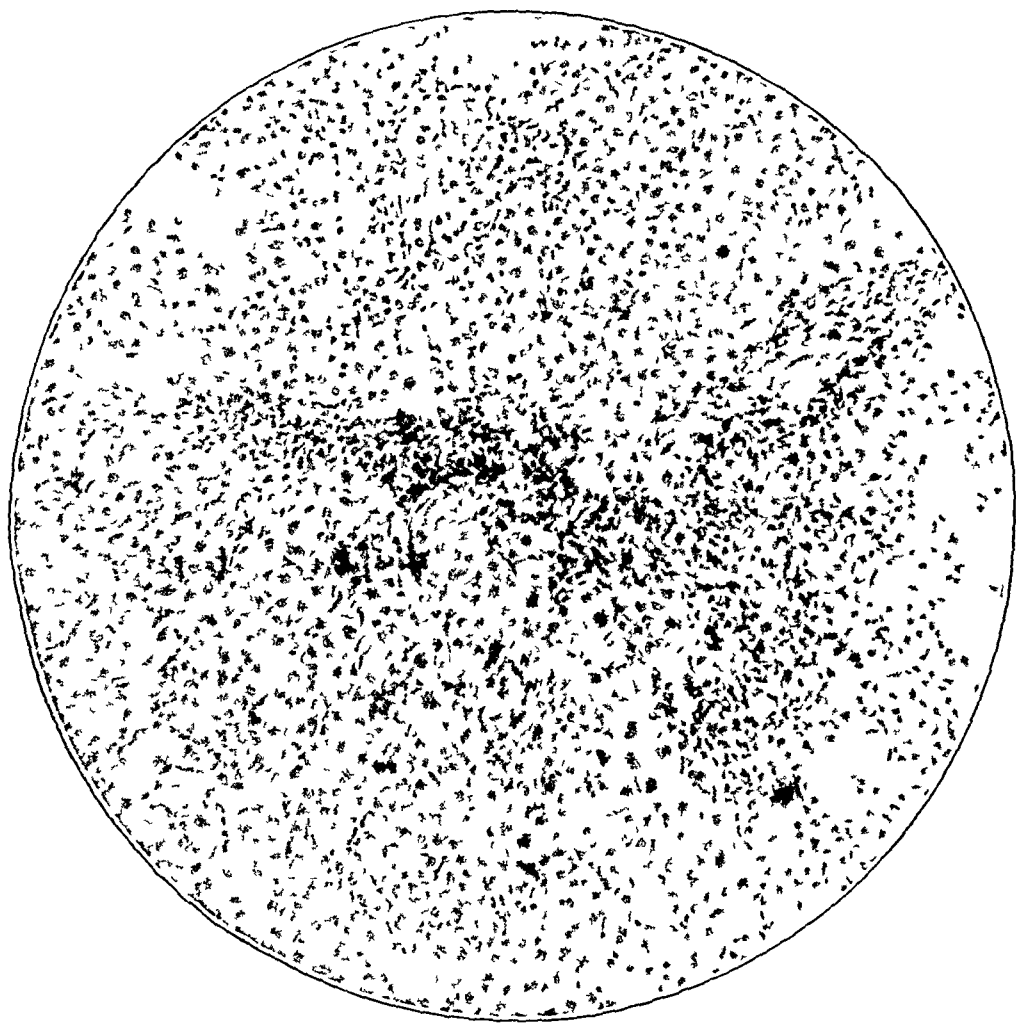


Fig 8—Biopsy specimen of the liver of a woman of 45 with subchronic atrophy of the liver, taken after one and three-quarters months' duration of symptoms The duration of the disease to death was fourteen months

In both groups of material, a few patients had perihepatitis as a sequela

11 Snell, A M Fundamentals in the Diagnosis of Jaundice, J A M A **138** 274-279 (Sept 25) 1948

12 Scheel, V Studies on Cholelithiasis, Ugesk f læger **73** 1756-1774, 1911 Hansen, S Cholelithiasis, *ibid* **84** 405-421, 1922 Wollesen, J M Pregnancy and Gallstone Formation, Thesis, Copenhagen, 1940

Microscopic Anatomy—Biopsy of the liver was carried out according to the method of Iversen and Roholm¹³ in 8 of the 108 cases of subchronic atrophy of the liver. Biopsy was undertaken after one, one and one-fourth, one and one-half, one and three-fourths, two, three, six and fourteen months of jaundice, respectively. The findings were the same in all instances and can be characterized as violent hepatitis (figs 7, 8 and 9). The trabecular plan was indistinct. A number of the parenchyma

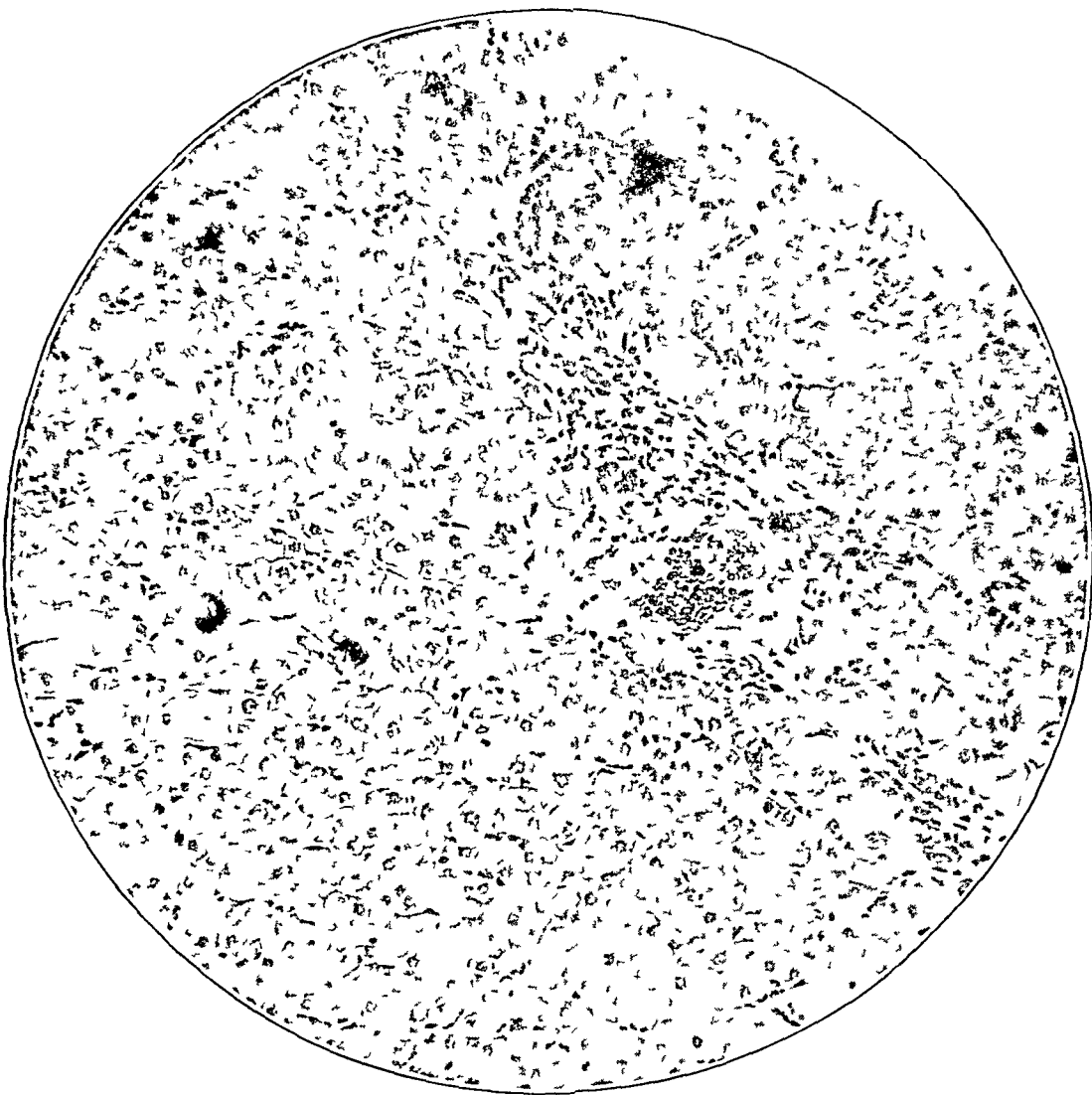


Fig 9—Biopsy specimen of the liver of a man of 36 with acute hepatitis, taken after two months duration of symptoms. A follow-up examination one month later showed no symptoms or signs of hepatic disease.

cells appeared strikingly large, with large nuclei. An intense infiltration of inflammatory cells was found in the periportal spaces, as well as interstitially in the parenchyma. The connective tissue in the periportal spaces was considerably increased in quantity. Bile pigment was found, mainly intracellularly, in the form of fine granules, but various accumu-

13 Iversen, P, and Roholm, K. An Aspiration Biopsy of the Liver, with Remarks on Its Diagnostic Significance, *Acta med Scandinav* **102** 1-16, 1939.

lations of bile pigment were also found in the form of elongated globules. There was nothing in the microscopic appearance of the liver in the cases of subchronic atrophy of the liver which distinguished it fundamentally from that in the cases of severe acute hepatitis, but in no instance of benign hepatitis did we find such great changes (especially in connection with intralobular cell infiltration) at such a late stage after the inception of the disease (fig 9).

Other Findings—*Icterus* By far the greater number of patients with subchronic atrophy of the liver died with icterus (94 of 105 patients, or 90 per cent), whereas only 11 patients died without icterus and had never had icterus at any stage of the hepatic disease. Compared with this figure, only 30 (41 per cent) of 74 patients with Laennec's cirrhosis had icterus at the time of death. This coincides with the fact that loss of hepatic function dominates the pathologic picture to a greater extent in subchronic atrophy of the liver than in Laennec's cirrhosis.

TABLE 1—*Disorders in Cases Complicated with Ascites*

Disorder	Cases of Subchronic Atrophy of the Liver	Cases of Laennec's Cirrhosis
Esophageal varices	40 (50%)	29 (72.5%)
Splenic enlargement	44 (55%)	22 (55%)
Hydrothorax	39 (48.7%)	17 (42.5%)
Edema of the legs	48 (60%)	25 (62.5%)
Lumbar edema	37 (46.2%)	.

As regards the degree of icterus there was also a difference, since one half of 94 patients having icterus together with subchronic atrophy of the liver had an icterus index (Meulengracht) above 40, whereas only one third of 30 patients with Laennec's cirrhosis had an index above 40 (the index was reckoned at the time of death).

Ascites Ascites was found at the autopsies of 80 patients (74.1 per cent) with subchronic atrophy of the liver, whereas only 40 patients (54 per cent) with Laennec's cirrhosis had ascites. As regards the degree of ascites, the distribution among the patients was as follows: 8 (10 per cent) had less than 0.5 liter of fluid, 48 (60 per cent) had between 0.5 and 2 liters and 24 (30 per cent) had over 2 liters. The percentage distribution was the same among the patients with Laennec's cirrhosis.

It is apparent from table 1 how often patients with subchronic atrophy of the liver or Laennec's cirrhosis complicated with ascites had the following disorders at the time of autopsy: esophageal varices, splenic enlargement, hydrothorax and edema of the legs and of the lumbar region.

The cause of ascites in portal cirrhosis is generally considered to be partly portal hypertension and partly low colloid osmotic pressure.

This hypothesis was first presented by Iversen¹⁴ In an earlier study with Brun,¹⁵ we investigated the colloid osmotic pressure in subchronic atrophy of the liver in order to determine the pathogenesis of ascites in this disease We found that all patients with ascites and edema had a colloid osmotic pressure below 220 to 240 mm of water, whereas those without ascites and edema had a higher colloid osmotic pressure Since, in addition, ascites usually occurs at the same time as edema of the legs and since ascites may completely disappear, it was concluded that low colloid osmotic pressure was the most essential factor in the pathogenesis of ascites It is still believed that low colloid osmotic pressure is the essential cause of ascites occurring in subchronic hepatitis In this series, however, postmortem findings showed that esophageal varices also appeared in 50 per cent of the cases of subchronic atrophy of the liver with ascites A certain degree of portal hypertension must therefore exist in this disease A closer analysis of the figures shows that esophageal varices are more frequent in Laennec's cirrhosis, just as their degree of development is greater in this disease, as will be indicated Thus there can be no doubt at all that portal hypertension is more developed in Laennec's cirrhosis than in subchronic atrophy of the liver

Splenic Enlargement Splenomegaly in the chronic diseases of the liver is thought, in general, to be caused by portal hypertension, McNee,¹⁶ however, stated that the enlargement can arise on a toxic basis The possibility that splenomegaly may be due to immunization processes must also be taken into consideration Subchronic atrophy of the liver is presumably a virus infection, and the occurrence of splenomegaly in infectious diseases and experimental immunization is a well known phenomenon¹⁷

In our postmortem material, of the subjects with subchronic atrophy of the liver 54 (50 per cent) had splenic enlargement, whereas it was not apparent in 54 Of the subjects with Laennec's cirrhosis, 56 per cent had splenic enlargement

14 Iversen, P Untersuchungen über die Ascitespathogenese, *Klin Wchnschr* **7** 2001-2004, 1928

15 Bjørneboe, M, Brun, C, and Raaschou, F Colloid Osmotic Pressure in Chronic Hepatitis, *Arch Int Med* **83** 539-546 (May) 1949

16 McNee, J W Liver and Spleen Their Clinical and Pathological Associations, *Brit M J* **1** 1111-1116, 1932

17 (a) Hellman, T, and White, G Das Verhalten des lymphatischen Gewebes während eines Immunisierungsprozesses, *Virchows Arch f path anat* **278** 221-257, 1930 (b) Rich A R Acute Splenic Tumor Produced by Non-Bacterial Antigens, *Proc Soc Exper Biol & Med* **32** 1349-1351, 1935 (c) Bjørneboe, M, and Gormsen, H Experimental Studies on the Role of Plasma Cells as Antibody Producers, *Acta path et microbiol Scandinav* **20** 649-692, 1943

With regard to the degree of splenic enlargement observed at autopsy in subchronic atrophy of the liver, 33 subjects had a slight degree of splenic enlargement (the volume was greater than 12 by 8 by 4 cm) Twenty had moderate splenic enlargement, the volume being greater than 15 by 10 by 6 cm, and only 1 patient had a large degree of splenic enlargement, with a volume greater than 20 by 12 by 8 cm The distribution was the same in among the patients with Laennec's cirrhosis, which in itself is remarkable, since it is presumed from the foregoing data that portal hypertension is more developed in Laennec's cirrhosis

Thirty-two of the 54 patients with splenic enlargement (51.8 per cent) did not have esophageal varices This figure permits the assumption that there really are causes of splenic enlargement apart from portal hypertension Splenic enlargement without esophageal varices appeared in only 24 per cent of the subjects with Laennec's cirrhosis, if one assumes that there are only the three aforementioned causes of spleno-

TABLE 2—*Degree of Severity of Esophageal Varices*

Degree	Cases of Subchronic Atrophy of the Liver	Cases of Laennec's Cirrhosis
(+)	1 (2.1%)	1 (2%)
+	26 (54.2%)	16 (38%)
++	18 (37.5%)	15 (36%)
+++	3 (6.2%)	10 (24%)

megaly, splenic enlargement arising on a toxic or immunologic basis plays a smaller part in Laennec's cirrhosis than in subchronic atrophy of the liver

Nearly all patients with subchronic atrophy of the liver and splenic enlargement had ascites at the same time (44 patients, or 81.5 per cent), whereas only 23 of 41 patients (56 per cent) with Laennec's cirrhosis had ascites at the same time as splenic enlargement

Esophageal Varices Esophageal varices were found in 48 subjects (44.4 per cent) with subchronic atrophy of the liver and in 42 (58 per cent) with Laennec's cirrhosis Only 1 subject (0.9 per cent) with subchronic atrophy of the liver died after rupture of the varix with hematemesis, whereas 5 (6.6 per cent) with Laennec's cirrhosis died after rupture This difference, too, indicates the greater degree of portal hypertension in patients with Laennec's cirrhosis, as do the figures in table 2, giving the degree of severity of esophageal varices for the two conditions

Hydrothorax The occurrence of hydrothorax in hepatic diseases is an argument for the existence and importance of low colloid osmotic

pressure if diseases of the heart, kidneys and lungs are excluded. Forty-two subjects (38.9 per cent) with subchronic atrophy of the liver and 24 subjects (32 per cent) with Laennec's cirrhosis had hydrothorax. Of the 42 subjects with subchronic atrophy of the liver, 13 had unilateral and 29 bilateral hydrothorax. Twenty of these had under 0.5 liter of fluid, 21 between 0.5 and 1 liter and 1 over 1.0 liter. Of the subjects with Laennec's cirrhosis only one fifth had more than 0.5 liter. Thus, as regards the degree of hydrothorax, a considerable difference is to be found between the two diseases.

A pronounced correlation exists between the occurrence of hydrothorax and that of ascites and edema, which points to the fact that low colloid osmotic pressure is a cause of ascites and edema. Of 42 subjects with subchronic atrophy of the liver and hydrothorax, 40 (95.3 per cent) had ascites at the same time, the great majority of these (69 per cent) had edema of the legs.

Edema of the Legs and the Lumbar Region. Information about the occurrence of edema of the legs in subchronic atrophy of the liver was given in 98 instances. In 52 patients (53.1 per cent) edema of the legs was observed during hospitalization, 92.4 per cent of these had ascites and 55.8 per cent hydrothorax.

Lumbar edema was observed in 29 (41.9 per cent) of 93 patients in whom the symptoms had been observed. Of these, 94.5 per cent had ascites and 52.8 per cent hydrothorax. Similar figures were recorded for patients with Laennec's cirrhosis. These figures indicate a close connection between ascites and edema.

Hemorrhagic Diathesis. An indication of a tendency toward hemorrhage was found at autopsy in 70 patients (64.8 per cent) with subchronic atrophy of the liver. Localization occurred in the following organs, in order of decreasing frequency: the pleura (43 patients), the pericardium (32), the endometrium (25), the intestines (17), the skin (13), the endocardium (8), the nose (4), the ovaries (1), the meninges (1) and the bile ducts (1).

Twelve patients (16 per cent) with Laennec's cirrhosis had a hemorrhagic tendency, thus, there exists a distinct difference between the diseases in this particular.

Since the prothrombin concentration was decreased in all patients with subchronic atrophy of the liver and hemorrhagic tendency, it is reasonable to assume that the hemorrhages are due to the decreased production of prothrombin in the liver, which is another indication that hepatic insufficiency is far more pronounced in subchronic atrophy of the liver than in Laennec's cirrhosis.

Among other causes of hemorrhagic tendency in hepatic diseases, thrombopenia¹⁸ must be mentioned and, especially so far as uterine hemorrhages are concerned, proliferation hemorrhage on the basis of the increased appearance of estrogens in the blood in cirrhosis of the liver¹⁹

Disorders of the Gastrointestinal Tract Gastric ulcer occurred in 11 (10.2 per cent) of the cases of subchronic atrophy of the liver. As a rule, completely fresh ulcers or erosive gastritis were concerned, in no case was there a chronic gastric ulcer. There is therefore little doubt that these gastric ulcers arise as a result of the disease of the liver. This connection has been suggested before, among other factors, by Schnitker and Hass²⁰. In this series, with Laennec's cirrhosis 19 per cent of 72 patients had gastric ulcer.

Of all the patients with hepatitis, 9 died of hematemesis and melena, only 1 of these had rupture of esophageal varices, whereas bleeding from the stomach in the others was due to gastric ulcer. In 2 cases the source of hemorrhage could not be established at autopsy.

Among those with Laennec's cirrhosis only 2 patients (2.6 per cent) with gastric ulcer and hematemesis were observed and 2 with cancer of the stomach.

Lucke⁷ mentioned that he found phlegmonous enteritis in the ileocecal part of the intestinal tract in 15 per cent of cases of acute yellow atrophy of the liver. There was no case with this complication in our epidemic.

Disorders of the Cerebrum²¹ The brain was examined microscopically in 8 cases of subchronic atrophy of the liver. In all edema of the brain was observed, and in 2 degeneration of the ganglion cells was noted. Lucke⁷ observed similar edema of the brain in acute yellow atrophy of the liver and perivascular and meningeal lymphocytic infiltrations in 15 per cent of the patients in his series. Decourt, Bertrand, Guillaumin and Gruner²² similarly stated the opinion that edema of the brain and degeneration of the ganglion cells play an important part in hepatic coma in acute yellow atrophy of the liver.

18 King, R. B. Blood Picture in Portal Cirrhosis of Liver. Report Based on One Hundred Cases, *New England J. Med.* **200** 482-484, 1929.

19 Biskind, M. S., and Biskind, S. R. Effect of Vitamin B Complex Deficiency on Inactivation of Estrone in the Liver, *Endocrinology* **31** 109-114, 1942.

20 Schnitker, M. A., and Hass, V. G. M. A Histological Study of the Liver in Patients Affected with Peptic Ulcer, *Am. J. Digest. Dis.* **1** 537-543, 1934.

21 Microscopic examinations of the brains were made by Dr. Erna Christensen.

22 Decourt, J., Bertrand, I., Guillaumin, C. D., and Gruner, J. Ictère aigu apyretique avec atrophie jaune aigue du foie. Rôle de l'œdème cérébral dans la pathogenie du coma terminal, *Bull. et mem. Soc. med. d'hôp. de Paris* **62** 33-37, 1946.

These changes must be assumed to be the underlying pathoanatomic cause of the neurologic symptoms in the clinical picture. In our material the symptoms were characterized by semiconsciousness to a varying degree over a period of several days, no excitation or convulsions were noted.

Disorders of the Bone Marrow Material was previously published by one of us on sternal punctures in 15 cases of chronic hepatitis,²³ data on some of which are included in the present material dealing with subchronic atrophy of the liver. The results are given in table 3.

The concentration of serum globulin was determined by the method of Henriques and Klausen.²⁴ The normal limits by this method are 1.7 to 3.1 Gm per hundred cubic centimeters.²⁵ Gormsen²⁶ indicated that by far the largest number of normal persons have less than 1 per cent of plasma cells in the sternal marrow but that amounts up to 3 per cent can be seen under normal conditions. It can be deduced from the table that there is a tendency toward the increase of plasma cells in the sternal

TABLE 3—*Concentration of Plasma Cells in Sternal Marrow and of Serum Globulin in 15 Cases of Chronic Hepatitis*

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Plasma cells, per cent of nucleated cells	4.5	4	4	3	3	3	2	2	2	2	2	2	2	1	1
Serum globulin, Gm /100 cc	5.5	6.1	3.8	5.3	5.1	5.1	2.9	4.3	4.5	5.5	3.2	3.5	4.1	2.8	2

marrow among these patients, and that the concentration of serum globulin shows a tendency to become greater with the increasing quantity of plasma cells in the sternal marrow. This discovery was compared with the hypothesis put forward by Bjørneboe and Gormsen^{17c} concerning the plasma cells as a place of production for the globulin of antibodies, and the opinion was formed that the investigations supported the view put forward previously,²⁷ namely, that the increase of serum globulin in hepatitis is connected with the formation of antibodies. Material on the basis of 24 sternal punctures undertaken in patients with chronic

23 Bjørneboe, M. Serum Protein Variations in the Course of Chronic Hepatitis, *Acta med Scandinav* (suppl 206) **130** 392-398, 1948. Examinations of the sternal marrow were made by Dr. H. Gormsen.

24 Henriques, V., and Klausen, U. Untersuchungen über den Serumalbumin- und Serumglobulingehalt des Serums unter wechselnden Umständen, *Biochem Ztschr* **254** 414-433, 1934.

25 Bing, J., Naeser, J., Rasch, G., and Roejel, K. Serum Proteins in Normal People, *Acta med Scandinav* **126** 351-369, 1946.

26 Gormsen, H. Study of Bone Marrow, Thesis, Copenhagen, 1942. Physicochemical Properties of Blood. Changes in Serum Proteins, Reduction in Oxygen Saturation of Arterial Blood, *Ann Int Med* **9** 690-711, 1935.

27 Snell, A. M. Effects of Chronic Disease of Liver on Composition and Physicochemical Properties of Blood. Changes in Serum Proteins, Reduction in Oxygen Saturation of Arterial Blood, *Ann Int Med* **9** 690-711, 1935.

hepatitis in the same epidemic²⁸ showed moderate hyperplasia of the marrow and a slight increase of plasma cells together with more or less pronounced erythroblastosis in a number of instances

CLINICAL SURVEY

Subchronic Atrophy of the Liver—The duration of disease was known in 98 cases (90.7 per cent of all the material). Far more of these patients than of those with Laennec's cirrhosis can as a rule give an account of the duration of the disease. On the average the duration was eight and two tenths months, the limits being one and thirty-two months (fig 10). In 48 cases (49 per cent) the duration was under five months, in 21 (19.5 per cent), it was over one year.

The disease begins with a preicteric phase, with anorexia, nausea, vomiting, lassitude and sometimes arthralgias. Jersild^{1b} showed that the preicteric phase is as a rule longer than in acute hepatitis.

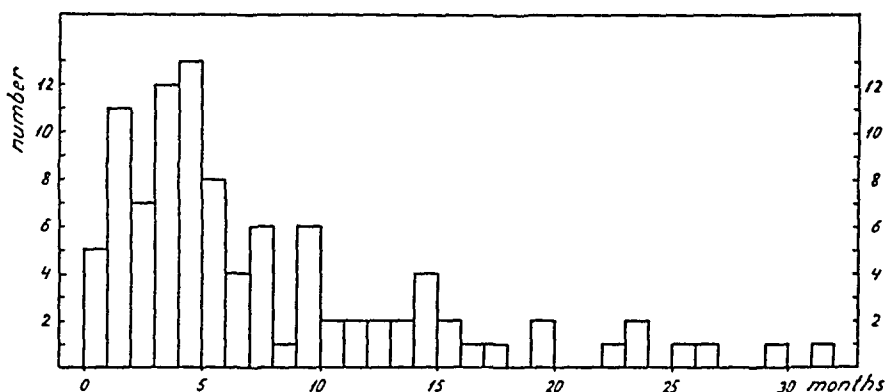


Fig 10—Duration of symptoms in subchronic atrophy of the liver

The patients then become icteric. The icteric phase is characterized in this disease by a high icterus index and long duration. Often the icterus disappears, to recur later one or more times (in 55 cases there was 1 relapse, in 23, 2, in 9, 3, and in 5, more than 3). As a rule the patients die icteric, only 10 patients (10 per cent) had no icterus at autopsy. These patients had had icterus at no other time during the course of the disease.

Ascites is a frequent complication, appearing very late in the disease. With the presence of ascites the prognosis as a whole is extremely poor, though a few patients do improve.²⁹

The duration of ascites was known in 49 cases (61.3 per cent) of those of subchronic atrophy of the liver. The duration was 26 cases,

28 Meulengracht, E., and Gormsen, H. Blood and Bone Marrow in Infective Subacute and Chronic Atrophy of the Liver, *Blood* **3** 1416-1425, 1948.

29 Bjørneboe, M. Serum Protein Variations in Chronic Hepatitis and the Clinical Course of the Disease, *Acta med Scandinav* **132** 170-180, 1948.

less than one month, 13, less than two, 5, less than three, and 5, more than three

A relatively large number of patients with subchronic atrophy of the liver had at one time or another pains in the epigastrium or in the right upper quadrant of the abdomen. Of 80 patients for whom information about this symptom was available, 36 (45 per cent) had pain. The existence of pains was not related to the observance of the sequela of perihepatitis.

The clinical picture is also characterized by anorexia and lassitude. Edema of the legs and the lumbar region frequently occurs with ascites. Sooner or later signs of hemorrhagic tendency arise and finally semi-consciousness, developing into coma.

Laboratory tests have shown that as a rule in this disease there are positive reactions to the Takata-Ara test³⁰ and the thymol turbidity test³¹ and low serum albumin and high serum globulin,²⁹ together with decreased prothrombin concentration in the blood, which is unaffected by the injection of water-soluble vitamin K preparations.^{1a} In a number of cases there has been an increase of iron in the blood serum,^{1a} decreased colloid osmotic pressure in the blood when ascites is present,¹⁵ moderate anemia, often with an increase in the diameter of erythrocytes and a tendency toward leukopenia.²⁸

Causes of Death Nearly all patients with subchronic atrophy of the liver died of loss of hepatic function with hepatic coma. Nine patients, as already mentioned, died of hematemesis and melena, 15 with pneumonia as a complication and 6 of other causes (hemiplegia, barbiturate poisoning, acute pancreatic necrosis and complications following cholecystectomy and gastric resection).

We have attempted to relate the frequency of hepatic coma in subchronic atrophy of the liver and Laennec's cirrhosis with the "volume index of the liver" which was calculated as indicated previously. It is apparent from figure 6 that the volume index in subchronic atrophy of the liver always lies below 3,000, whereas only 63 per cent of the patients with Laennec's cirrhosis had a volume index below 3,000. Hepatic coma appears, as already mentioned, as the cause of death of practically all patients with subchronic atrophy of the liver, whereas at most 43 per cent of the patients with Laennec's cirrhosis died of hepatic coma. It can be seen from figure 6 that hepatic coma occurs mainly in the patients having the lowest volume index of the liver.

According to these data, it is presumably legitimate to relate small hepatic volume and hepatic coma, moreover, the relation appears to be fairly obvious.

³⁰ Footnote 1, *a*, *b* and *c*

³¹ Marner, I. L. The Thymol Reaction as a Liver Test, *Acta med. Scandinav.* **131** 180-192, 1948

No relation was found between the duration of symptoms and the volume index of the liver in subchronic atrophy of the liver

Laennec's Cirrhosis—Evidence of previous syphilis was found in 16 per cent of these patients, the corresponding figure for those with subchronic atrophy of the liver was 2.8 per cent. Alcoholism was observed in 8 per cent. None of the patients with subchronic atrophy of the liver was addicted to alcohol. Former icterus (i. e., at least a year before the first symptom of hepatic cirrhosis) was noted in 6 cases (8 per cent), whereas none of the patients with subchronic atrophy of the liver had had icterus previously. This figure must certainly be taken as a minimum, since the case records were often incomplete on these points. An indication can be seen, however, of the well known fact that syphilis and alcoholism are found relatively often among patients with cirrhosis of the liver. On this point, subchronic atrophy of the liver seems to differ from Laennec's cirrhosis.

The duration of symptoms was evident in only 44 (58 per cent) of the cases of Laennec's cirrhosis as against 90.7 per cent of those of subchronic atrophy of the liver, the information offered was in many cases uncertain. It is characteristically difficult to determine the time of onset of the disease in Laennec's cirrhosis, in contrast to subchronic atrophy of the liver. In 23 cases (30 per cent) the duration of symptoms was under five months, in 7 (9.2 per cent) it was over twelve months. Thus, no striking difference in the duration of symptoms was discovered, even though among the cases of Laennec's cirrhosis there were relatively more with a duration of symptoms of five to twelve months. There was information about the first symptom in 44 (58 per cent) of the cases. In order of descending frequency, the first symptoms were as follows: icterus, ascites, lassitude, dyspepsia, edema, pains in the region of the liver, diarrhea and hematemesis. Ten patients (9 women and 1 man) occupied an exceptional position in regard to symptoms, since the course of their illness corresponded completely to that of subchronic atrophy of the liver. When these patients are not included in the material a different order is obtained in the symptoms mentioned, namely, ascites, edema, lassitude, dyspepsia, icterus, pains, diarrhea and hematemesis. This order in regard to frequency corresponds more closely with what is generally indicated in the literature on the subject.³²

³² The distribution according to sex shows, as in other material in Laennec's cirrhosis, a preponderance of men. It is not especially marked, however. As has already been mentioned, 10 patients occupied a special position in having a course of symptoms as in subchronic atrophy of the liver. If these patients are not included in the material a sex distribution of 24 women and 42 men is obtained, more closely related to the sex distribution of other series and to that of the material from previous years from Kommunchospitalet (fig. 4).

The 10 patients with Laennec's cirrhosis already mentioned, who clinically presented the appearance of subchronic atrophy of the liver, had symptoms the duration of which did not differ fundamentally from the duration of symptoms in subchronic atrophy of the liver (5 patients, less than five months, 3 patients, more than twelve months). Thus, we were not able in our material to find a basis for the assumption previously advanced³³ that specially prolonged cases of subchronic atrophy of the liver present the appearance of Laennec's cirrhosis pathoanatomically.

As mentioned previously, 40 (54 per cent) of the subjects had ascites when the autopsy was made. The duration was determined for only 21, of whom 7 had ascites less than one month, 6, less than two months, 4, less than three months, and 4, more than three months. On this point there was no difference in the two types of material. In Laennec's cirrhosis the occurrence of ascites is a very bad sign for prognosis, as is well known.

In 20 cases there was evidence of pains in the epigastrium or in the right upper quadrant. This number represents scarcely half the cases in which the symptom was known to exist. In this factor there was no difference in the two types of materials.

Causes of Death. Of the patients with Laennec's cirrhosis, at most 33 (43 per cent) died of hepatic coma, as previously mentioned. It has already been stated that this is a considerably lower frequency than in subchronic atrophy of the liver. In 9 cases the diagnosis of coma was uncertain, in 8 of these an infection was found at the same time, and the death of the ninth patient was in connection with a cholecystectomy.

The other causes of death were as follows: bleeding from esophageal varices, 5 patients; bleeding from gastric ulcer, 2; primary cancer of the liver, 5; portal thrombosis, 2; cardiac insufficiency, 8; cancer with different localizations, 6; resection for cancer of the stomach, 2; pneumonia, 4; and different causes, 9. In the last group the causes were the following: nephritis with uremia, tumor of the spinal cord, cholecystectomy complicated with peritonitis, fracture of the femur, fracture of the skull, cerebral hemorrhage and pulmonary embolism (1 patient each) and prostatic hypertrophy with pyelonephritis (2 patients).

Heart diseases in the material will be dealt with more closely. As already indicated, 8 patients died of cardiac insufficiency. The frequency of pathologic conditions of the heart was, however, much greater. When the milder variations, such as a slight degree of coronary arteriosclerosis, cardiac hypertrophy or sequels to endocarditis, were disregarded the figures in table 4 were obtained.

³³ Faber, M. Note on Porto-Caval Anastomoses, *Ugeskr. f. læger* **108** 928 1946.

In all, 46 patients (61 per cent) of the 76 with Laennec's cirrhosis were found to have these variations. This was a considerably higher frequency than in the cases of subchronic atrophy of the liver, in which the following variations were observed:

These variations were noted in 30 subjects in all (28 per cent). The most striking difference in the two groups of material with regard to these changes is the difference in the occurrence of cardiac hypertrophy, which is connected with the fact, established by Raaschou,³⁴ that there are strikingly few patients with arterial hypertension among

TABLE 4—*Pathoanatomic Changes in the Heart in Laennec's Cirrhosis*

Change	No. of Cases
Cardiac hypertrophy	19
Coronary arteriosclerosis	25
Occlusion of the coronary artery	2
Mitral stenosis	2
Aortic stenosis	1
Pericardial adhesions	4
Acute pericarditis	4
Subacute endocarditis	1
Syphilitic aortitis	3
Myocardial fibrosis	1

TABLE 5—*Pathoanatomic Changes in the Heart in Subchronic Atrophy of the Liver*

Change	No. of Cases
Cardiac hypertrophy	2
Coronary arteriosclerosis	25
Occlusion of the coronary artery	1
Sequel to mitral endocarditis	1
Pericardial adhesions	1
Myocardial fibrosis	2

those with subchronic atrophy of the liver. Among the subjects with Laennec's cirrhosis, one third had arterial hypertension (as indicated by a systolic blood pressure of over 150), a figure which corresponds with normal findings in postmortem material within these age ranges.³⁴

On the whole, the impression was gained that the causes of death in the subjects with Laennec's cirrhosis were distributed, as might have been expected, among a set of people in this age group. The impression was also given that only in a minority (especially those with the smallest livers) was hepatic disease a direct cause of death through hepatic coma, rupture of esophageal varices or portal thrombosis. Corresponding to

³⁴ Raaschou, F. Blood Pressure and Heart Weight in Chronic Hepatitis, *Nord med* 42: 1791-1795, 1949.

this, the diagnosis in subchronic atrophy of the liver is nearly always made during life, while only in 23 (29 per cent) of the cases of Laennec's cirrhosis was cirrhosis suspected before autopsy

COMPARISON OF SUBCHRONIC ATROPHY OF THE LIVER AND LAENNEC'S CIRRHOSIS

The differences, apart from the appearance of the liver, in the pathologic picture and the clinical aspect of subchronic atrophy of the liver and Laennec's cirrhosis may be briefly summarized

1 Nearly all patients with subchronic atrophy of the liver are women, whereas there is a preponderance of men as far as Laennec's cirrhosis is concerned

2 The impression is obtained that portal hypertension is more pronounced in Laennec's cirrhosis than in subchronic atrophy of the liver, since the esophageal varices are more frequent and more pronounced in Laennec's cirrhosis, just as the frequency of rupture of the varices is greater in this disease

3 It is our opinion that the low colloid osmotic pressure dominates the clinical picture more in subchronic atrophy of the liver than in Laennec's cirrhosis, since the frequency of ascites and the degree of hydrothorax found at autopsy are greater in subchronic atrophy of the liver than in Laennec's cirrhosis

4 Pronounced impairment of hepatic function is more frequent in subchronic atrophy of the liver, as may be seen from the fact that hemorrhagic tendency and death from hepatic coma are far more frequent in this disease than in Laennec's cirrhosis

The size of the liver, expressed as its volume index, is on the average smaller in subchronic atrophy of the liver than in Laennec's cirrhosis, which presumably is the cause of the greater frequency of hepatic coma in the former. The frequency of hepatic coma is greater in subjects with Laennec's cirrhosis with a low volume index than in those with a high volume index, which also supports this assumption

5 In addition, the following factors are allied with these differences

1 A greater frequency of syphilis, alcoholism and icterus in anamnesis (i e, more than a year before the first symptom) occurs in Laennec's cirrhosis. 2 Gallstones and heart disease (especially cardiac hypertrophy) occur in greater frequency in Laennec's cirrhosis (primary carcinoma of the liver and hepatomas do not occur at all in subchronic atrophy of the liver, in contrast to Laennec's cirrhosis). 3 In the great majority of cases of subchronic atrophy of the liver evidence as to the duration of symptoms can be obtained from the patient, whereas this happens far less often in Laennec's cirrhosis. 4 Laennec's cirrhosis was not diagnosed during life in three quarters of the cases,

but since 90 per cent of patients with subchronic atrophy of the liver have jaundice during life this condition can usually be recognized clinically as a hepatic disease. 5 The frequency and degree of enlargement of the spleen are identical in subchronic atrophy of the liver and Laennec's cirrhosis. However, there are more cases of enlargement of the spleen without esophageal varices in subchronic atrophy of the liver. To sum up, one may state that subchronic atrophy of the liver leads to a greater degree of reduction of the liver parenchyma than does Laennec's cirrhosis. From the clinical point of view, a greater frequency of symptoms of loss of hepatic function and a greater frequency of death from hepatic coma are in accord with this conclusion.

SUMMARY

The cases of subchronic atrophy of the liver described in the literature up to the time of writing have been chiefly isolated cases appearing in case materials of acute yellow atrophy of the liver.

The present work is based on autopsy material consisting of 108 cases of subchronic atrophy of the liver and 76 cases of Laennec's cirrhosis.

Material—Subchronic Atrophy of the Liver. The material consisted of 108 subjects (6 men and 102 women) on whom autopsy was undertaken from Jan. 1, 1944 to Jan. 1, 1948. Practically all the patients died after their fortieth year.

Laennec's Cirrhosis. The material consisted of 76 subjects (43 men and 33 women). The age range corresponded to that in subchronic atrophy of the liver.

Frequency. An examination of the collected postmortem material at Kommunehospitalet from 1928 to 1947 inclusive showed that the number of cases of Laennec's cirrhosis was more or less constant, whereas instances of subchronic atrophy of the liver appeared only sporadically before 1944.

Pathologic Anatomy—The macroscopic and microscopic pathologic anatomy of the disease is described according to the literature.

The microscopic anatomy of the liver on biopsy corresponded to that of acute hepatitis of severe degree.

The weight of the liver in most cases was found to be reduced to below half the normal weight.

A fairly exact correlation was found between the weight of the liver and the volume index of the liver (determined by multiplication of the three dimensions).

The volume index of the liver in subchronic atrophy of the liver showed a smaller variation than that in Laennec's cirrhosis. The reduction of the liver parenchyma was generally more pronounced in subchronic atrophy of the liver.

Icterus appeared in 90 per cent of the patients with subchronic atrophy of the liver at the time of death, whereas 10 per cent died without icterus and without having had icterus at any stage of the disease. Only 41 per cent of the patients with Laennec's cirrhosis had icterus at the time of death.

Ascites occurred in 74.1 per cent of the patients with subchronic atrophy of the liver and in 54 per cent of those with Laennec's cirrhosis. No difference in the degree of ascites was observed in the two diseases.

The pathogenesis of ascites is discussed, and it is emphasized that the reduced colloid osmotic pressure is regarded as the dominant factor in subchronic atrophy of the liver. The occurrence of mild esophageal varices in half the cases, however, indicated that slight portal hypertension also occurs in this disease.

Enlargement of the spleen was a symptom which appeared with equal frequency (in about half the cases) in these diseases, the degree of enlargement of the spleen was also identical. Enlargement of the spleen without esophageal varices was somewhat more frequent in subchronic atrophy of the liver, which is expressive of the fact that enlargement of the spleen arising on a toxic or immunologic basis may possibly play a greater part in this disease than in Laennec's cirrhosis.

Esophageal varices were found in 44.4 per cent of the subjects with subchronic atrophy of the liver and in 58 per cent of the subjects with Laennec's cirrhosis. In the latter disease they were more pronounced. This, together with the more frequent occurrence of rupture of varices in Laennec's cirrhosis, indicated that portal hypertension is more pronounced in the latter disease.

Hydrothorax was of almost equal frequency at the time of death in the two diseases (it occurred in 38.9 per cent of the subjects with subchronic atrophy of the liver and in 32 per cent of those with Laennec's cirrhosis). Greater degrees of pleural effusion were found in subchronic atrophy of the liver than in Laennec's cirrhosis. In subchronic atrophy of the liver there is a pronounced correlation between the occurrence of hydrothorax and that of ascites and edema, which supports the assumption that low colloid osmotic pressure is a cause of ascites and edema.

Edema of the legs was found at death to be of equal frequency in these diseases (it occurred in at least half the cases).

A hemorrhagic tendency was observed far oftener in subchronic atrophy of the liver than in Laennec's cirrhosis (in 64.8 per cent of the subjects as against 16 per cent). This difference in frequency is related to the reduced prothrombin content of the blood and to the more frequent occurrence of loss of hepatic function in subchronic atrophy of the liver.

Gastric ulcer was found in 10.2 per cent of subjects with subchronic atrophy of the liver and in 2.6 per cent of those with Laennec's cirrhosis. In many instances the ulcers bled and caused hematemesis and melena.

In the microscopic examination of the brain in subchronic atrophy of the liver, cerebral edema and, in some cases, degeneration of the ganglion cells were discovered.

When the sternal marrow was examined, a slight tendency toward increase was observed in the plasma cells.

Hepatomas and primary carcinoma of the liver were not found at all in the subjects with subchronic atrophy of the liver, whereas they appeared in some with Laennec's cirrhosis.

Gallstones appeared less often in subchronic atrophy of the liver than in Laennec's cirrhosis.

Clinical Aspects—*Subchronic Atrophy of the Liver* The duration of the symptoms in the present series was on the average eight and two tenths months, varying from one to thirty-two months. The course of the disease is characterized by a long preicteric period and by an icteric phase which consists of several waves of icterus in succession (in 37 cases there was more than 1 relapse of icterus in the course of the disease). Ascites occurs late in the disease. In more than half the cases in which evidence was given of the duration of ascites, there was at most one month between the occurrence of ascites and death. Pains in the epigastric region or in the right upper quadrant were noted in barely half the cases. Edema occurred as a rule at the same time as ascites, sooner or later a hemorrhagic tendency appeared, and finally semiconsciousness developed into coma. Nearly all the patients forming the material died of hepatic coma (9 died of hematemesis and melena, 15 with complicating pneumonia and 6 of other causes). The frequent occurrence of hepatic coma and of small volume index of the liver are related to each other.

Laennec's Cirrhosis Syphilis, alcoholism and previous icterus (occurring more than one year before the first symptom) were frequent in anamnesis among patients with Laennec's cirrhosis and among those with subchronic atrophy of the liver. Evidence as to duration of the disease was given less often by patients with Laennec's cirrhosis than by those with subchronic atrophy of the liver. In the cases in which such evidence was given, there was no certain difference in the duration of symptoms between the two types of material. The initial symptoms were as follows, in order of decreasing frequency: icterus, ascites, lassitude, dyspepsia, edema, pains in the region of the liver, diarrhea and hematemesis. In Laennec's cirrhosis there was a short interval between the occurrence of ascites and death. Pains in the region of the liver were noted with the same frequency as in the material for subchronic atrophy of the liver—in almost half of

the cases The cause of death was hepatic coma in 33 cases (43 per cent) , in 9 of these, however, the diagnosis of coma was uncertain The instances of coma occurred mainly among patients with a small volume index of the liver, which observation strengthens the assumption that it is the reduction in quantity of hepatic cells which causes the loss of hepatic function The remaining causes were distributed over a series of different diseases characteristic for the age groups included in the material There was a pronounced difference in the frequency of hypertrophy of the heart in the two groups of material In Laennec's cirrhosis hypertrophy of the heart was observed in one quarter of the subjects, whereas it was observed in only 2 of the 108 subjects with subacute atrophy of the liver This circumstance was presumably due to the fact that arterial hypertension is remarkably rare in patients with subacute atrophy of the liver

To sum up, it can be stated that subacute atrophy of the liver leads to a greater degree of reduction of the liver parenchyma than does Laennec's cirrhosis Clinically a greater frequency of symptoms of loss of hepatic function is in accord with this, as is a greater frequency of death from hepatic coma

ANEMIA ASSOCIATED WITH CIRRHOSIS OF THE LIVER

Study of Thirty-Two Cases

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MACROCYTIC anemia associated with cirrhosis of the liver has been repeatedly observed in Western countries. Assuming that the function of the liver plays a part in normal erythropoiesis, Van Duyn^{1b} stated the belief that the pathologic changes in that organ might be held indirectly responsible for the development of the macrocytic blood picture. Davidson and Fullerton² suggested that the macrocytic anemias of hepatic disease are caused by failure of the final stages of synthesis of the hemopoietic principle rather than by failure to store the substance.

Goldhamer and his associates³ observed that an extract prepared post mortem from the liver of a patient with cirrhosis and macrocytic anemia was ineffective in eliciting a hemopoietic response when administered parenterally to a patient with pernicious anemia in relapse. This observation with other experimental data led them to conclude that the specific hemopoietic substance might not be stored by a severely damaged liver or, even though stored, might not be delivered to the tissues.

Offering contrary evidence was the work of Schiff and his associates,⁴ who prepared extracts from the livers obtained post mortem from 5 patients with clinical hepatic disease. There were 2 patients with portal cirrhosis, 1 with obstructive cirrhosis secondary to neoplasm of the hepatic duct, 1 with chronic passive congestion and 1 with extensive leukemic infiltration. The extracts were administered intramuscu-

From the Central University Medical School

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2 Davidson, L. S. P., and Fullerton, H. W. *Quart J Med* **7** 43, 1938.

3 Goldhamer, S. M., Isaacs, R., and Sturgis, C. C. *Am J M Sc* **188** 193, 1934.

4 Schiff, L., Rich, M. L., and Simon, S. D. *Am J M Sc* **196** 313, 1938.

larly to a suitably controlled group of patients with pernicious anemia in relapse. Characteristic reticulocytosis resulted, followed by an increase in hemoglobin concentration and in red cell count and by marked clinical improvement. The 3 patients with cirrhosis had macrocytic anemia, whereas the type of anemia in the remaining 2 cases was not definitely determined. The authors therefore concluded that the human liver may contain the specific hemopoietic principle even when it is the seat of extensive and protracted disease. This holds true even in the presence of macrocytic anemia, strongly suggesting that the macrocytic anemia associated with hepatic disease is not caused by failure of the liver to store the specific antianemic substance.

The fact that hepatic damage may be associated with macrocytic anemia is established, yet, the question of the mechanism of macrocytosis is still not settled at the time of writing. In China, cirrhosis of the liver is rather common. It is hoped that this study of the anemia associated with the disease may throw some light on the macrocytosis.

MATERIAL AND METHODS

The material consisted of 32 cases of typical cirrhosis of the liver, diagnosis in 4 of which was verified by biopsy. The hemoglobin concentration was determined with Sahli's hemometer, the red corpuscle count, with the improved Neubauer bright line hemacytometer, the hematocrit reading, by Wintrobe's method, and the mean corpuscular diameter by the direct measurement method of Price-Jones on 500 corpuscles. Sternal puncture was performed in 19 cases to determine the presence of the megaloblasts of Ehrlich.

DATA

The anemia in all cases was of the normocytic type except in 2 (case 4 and case 32), in which there was macrocytosis with a mean corpuscular volume of 112 and 114 cubic microns, respectively, and a mean corpuscular diameter of 8.023 and 8.461 microns, respectively. In none of the 2 cases of macrocytic anemia or the 17 in which a sternal puncture was made was the presence of a typical megaloblast observed, but in case 4 the presence of hyperplastic normoblasts was determined. The details are presented in the accompanying table.

COMMENT

Since the improved morphologic study of the red corpuscles developed, anemia has been classified into normocytic, microcytic and macrocytic types. Whenever the mean corpuscular volume in a case of anemia is found to be greater than 94 cubic microns, the disease is macrocytic⁵. The cause is usually one of the following: (1) lack of intake of the extrinsic factor of Castle, as in tropical macrocytic anemia, (2) absence of the intrinsic factor of Castle, as in typical pernicious

⁵ Whitby, L. E. H., and Britton, C. J. C. Disorders of the Blood, ed. 4. Philadelphia, P. Blakiston's Son & Co., 1944, p. 1450.

Blood Data

No	Age, Yr	Sex	Evidence of Cirrhosis of Liver	Red Blood Cells, Millions/Cu Mm	Hemo globin Value, Gm/100 Cc	White Blood Cells, per Cu Mm	Hemato crit Reading, Per centage	Mean Corpus Volume, Cu u	Mean Corpus cular Hemo globin Concen tration, Per centage	Price-Jones Curve			Sternal Marrow
										Mean Corpus Diameter	Standard Deviation	Variation Per centage	
1	32	M	Ascites, enlarged spleen, dilated abdominal veins	2.15	5.0	1,950	18.0	84.0	23.5	7.264	0.990	13.5	—
2	67	M	Ascites, enlarged spleen	2.31	7.7	7,000			33.0	7.552	0.984	13.0	—
3	54	M	Ascites, enlarged spleen, jaundice	3.45	9.8	4,200	33.0	95.6	28.7	7.695	0.758	9.9	—
4	54	M	Ascites, enlarged spleen, dilated abdominal veins	2.22	8.4		25.0	112.0	37.0	8.023	0.848	10.6	—
5	28	M	Ascites, enlarged spleen, dilated abdominal veins	2.53	7.5		23.6	91.0	29.3	7.831	0.899	11.5	—
6	59	F	Ascites, enlarged liver and spleen, dilated abdominal veins	3.62	10.2		33.3	90.2	28.0	7.401	0.782	10.3	—
7	25	M	Ascites, enlarged liver and spleen, dilated abdominal veins	1.89	12.5		35.0	80.4	28.7				—
8	45	M	Ascites, enlarged spleen, dilated abdominal veins	3.17	9.9	6,400	31.0	97.8	31.3	7.718	1.190	15.4	—
9	32	M	Ascites, enlarged spleen, dilated abdominal veins	3.60	12.6		33.0	91.6	30.0				—
10	14	M	Persistently enlarged liver and spleen	2.82	7.3		28.0	99.0	25.7	7.563	0.970	12.6	—
11	30	M	Jaundice, ascites, dilated abdominal veins	3.73	12.3		32.0	95.0	31.2	7.733	0.760	10.2	—
12	24	M	Ascites, enlarged spleen, dilated abdominal veins, cirrhosis proved by biopsy	3.63	10.9		31.5	86.8	30.0	6.868	0.803	11.6	—
13	27	M	Ascites, dilated abdominal veins, jaundice	2.25	4.1		22.2	90.0	19.0	7.518	1.038	13.8	—
14	44	M	Ascites, enlarged spleen, dilated abdominal veins	3.15	7.6		27.6	97.6	24.1	6.916	0.810	11.7	—
15	27	M	Ascites, enlarged spleen, cirrhosis proved by biopsy	2.76	8.8	3,000	23.0	84.0	31.7	7.177	0.810	10.8	—
16	46	F	Ascites, enlarged spleen, dilated abdominal veins, hematemeses							6.716	0.886	13.2	—
17	42	M	Ascites, enlarged spleen, dilated abdominal veins	3.30	9.2		25.0	75.8	27.8	7.520	0.810	10.8	—
18	35	M	Ascites, enlarged spleen, dilated abdominal veins, hematemeses	2.38	7.7		22.0	94.5	32.3	7.598	0.830	10.9	—
19	65	M	Ascites, enlarged liver and spleen, dilated abdominal veins	3.10	10.5	4,000	28.0	90.0	33.9	7.846	0.421	5.3	—
20	42	F	Persistently enlarged spleen	2.58	7.0		26.0	100.8	27.0	7.783	1.006	12.9	—
21	57	F	Biliary cirrhosis discovered during cholecystectomy	3.70	12.5		35.0	95.0	34.0	7.318	0.717	9.8	—
22	40	M	Ascites, enlarged spleen, dilated abdominal veins	3.50	10.5		23.3	92.3	30.0	7.148	0.921	12.9	—
23	29	M	Ascites, enlarged spleen, dilated abdominal veins	3.63	13.0		35.0	96.0	31.5	7.519	0.749	9.8	—
24	24	M	Ascites, enlarged spleen, dilated abdominal veins, hematemeses, jaundice	3.74	11.9		34.5	91.4	31.8	7.721	0.900	11.0	—
25	22	M	Ascites, enlarged spleen, dilated abdominal veins, jaundice	3.80	10.9		36.0	94.7	28.6	7.695	0.880	11.4	—
26	27	M	Enlarged spleen	3.39	10.5		32.0	74.4	30.9	7.673	0.910	12.0	—
27	24	M	Ascites, enlarged spleen	3.40	9.8		23.5	83.8	28.8	7.557	0.673	8.9	—
28	44	M	Progressively enlarged liver and spleen, jaundice, ascites							7.461	1.000	13.0	—
29	34	M	Ascites, dilated abdominal veins	3.51	11.2		32.0	91.1	31.8	7.703	0.630	8.8	—
30	29	F	Jaundice, enlarged liver and spleen, early cirrhosis proved by biopsy	3.24	10.5		31.0	96.0	32.1	7.841	0.800	11.0	—
31	28	M	Ascites enlarged spleen dilated abdominal veins	2.80	7.5		26.0	92.9	26.9	7.652	0.770	10.9	—

anemia, (3) poor absorption of the hemopoietic principle, as in idiopathic steatorrhea, (4) poor storage of the principle in the liver, as in cirrhosis of the liver, or (5) lack of utilization of the principle, as in the achrestic anemia of Israels and Wilkinson⁶ In short, all macrocytic anemias are supposed to be due to one single cause, that is, deficiency of the hemopoietic principle

Recent developments, however, suggest that not all macrocytic anemias are caused by such a deficiency According to this concept, two types may be distinguished

One is the megaloblastic type, which is due to deficiency of the hemopoietic principle This deficiency results in abnormal erythropoiesis which gives rise to the production of megaloblasts of Ehrlich (partly or completely hemoglobinized cells two to four times the size of an ordinary normocyte, the nuclei of which, though larger than those of normoblasts, do not occupy so much of the cell area, are finely reticulated and stain faintly⁷) and, in turn, to macrocytosis With liver therapy the megaloblastic hemopoiesis gives way to normoblastic hemopoiesis, and the anemia and macrocytosis subside The diagnosis of this type of anemia should be based on the presence of macrocytosis and of megaloblasts in the bone marrow and the peripheral blood, and on a good response to liver therapy

The other type is the macrocytic anemia occurring in severe hemolysis, certain types of aplastic anemia or diseases of the liver in which there is hyperplasia of the hemopoietic tissue evidenced by the presence of hyperplastic normoblasts, as described by Zanaty⁸ and Israels⁹ These are large cells, but never equal in size to the megaloblasts, their nuclei occupy most of the cell area, and the maturation of the nuclei always precedes that of the cytoplasm, namely, the cells undergo pyknosis before complete hemoglobinization of the cytoplasm occurs, whereas the nuclei in megaloblasts are always less mature than the cytoplasm The presence of these cells in the bone marrow does not indicate a deficiency of the hemopoietic principle but an increased demand on the normal hemopoietic tissue, which, in response to the call, puts out the hyperplastic normoblasts, which results in a slight or moderate degree of macrocytosis This macrocytic anemia is not improved by liver therapy

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8 Zanaty, A F *Lancet* 2 1365, 1937

9 Israels, M C G *Lancet* 2:207, 1941

It is not easy to make a distinction between a megaloblast and a hyperplastic normoblast, the latter frequently having been taken for a megaloblast. For instance, Janet M. Vaughan¹⁰ took such a hyperplastic normoblast, observed in a case of leukoerythroblastic anemia, to be a megaloblast. The close scrutiny of one smear, kindly given us by her, convinced us that the large cells were not megaloblasts. We also saw 2 patients with these cells. One had extremely severe, fatal macrocytic anemia of the aplastic type, due to the toxic effect of sulfonamide drugs and neoarsphenamine, which showed no response to the administration of iron or liver. The other had Marchiafava-Micheli syndrome with macrocytosis which showed no definite response to liver therapy, but there was a spontaneous remission. At first, we took these cells to be megaloblasts, but having read recent articles on them we believe they are hyperplastic normoblasts.

Although the distinction is sometimes difficult, the separation of these two types of macrocytic anemia (megaloblastic and hyperplastic) is of practical value, for it clears away a good deal of confusion in hematology and helps one to understand better the mechanism of macrocytosis. For instance, Hill and Hausmann,¹¹ in 1943, reported a case of macrocytic anemia secondary to acute hepatitis and supposed to have been cured by liver extract. Casual reading may convince one that that case supports the view that hepatitis causes deprivation of the hemopoietic principle and gives rise to megaloblastic anemia which responds to the administration of liver extract. The authors did not, however, determine the mean corpuscular volume of the red cells, though the color index was 1.37, they neglected the significance of the absence of megaloblasts of Ehrlich in the sternal marrow and of the slow response to the administration of liver extract (it took fifty-two days to raise the red cell count from 2,300,000 to 4,400,000 with liver extract). These facts plus the knowledge of two types of macrocytic anemia make us skeptical about the relation between this anemia and the deficiency of the hemopoietic principle. Appreciating the difference between the two types, Zanaty⁸ stated the belief that achrestic anemia is a special form of aplastic anemia in which there is hyperplasia of the bone marrow, resulting in the production of large normoblasts, and that, of course, that type of macrocytic anemia does not respond to liver extract.

Our 32 patients all had normocytic anemia except 2, who had macrocytic anemia but without the presence of megaloblasts in the marrow. One of them, however, had hyperplastic normoblasts in the

10 Vaughan, J. M. *The Anaemias*, ed. 2, New York, Oxford University Press, 1936, p. 139, plate 3, opposite p. 158.

11 Hill, J. N., and Hausmann, W. *Brit. M. J.* 2: 262, 1943.

marrow These cases strongly suggest that deficiency of the hemopoietic principle is not of significance in the anemias associated with cirrhosis of the liver, for there would likely have been at least a few cases of megaloblastic anemia among the 32 should cirrhotic change interfere with the storage of the hemopoietic principle

Wintrobe,¹² in his book on "Clinical Hematology," states "While it is undoubtedly true that cirrhosis of the liver and pernicious anemia may sometimes occur in the same individual, this explanation cannot account for the majority of the cases of macrocytic anemia under discussion [macrocytic anemia associated with disease of the liver]" We quite agree with his view We believe that some examples of macrocytic anemia associated with cirrhosis of the liver in Western countries are of the megaloblastic type, that is, due to a lack of the hemopoietic principle, and that they occur coincidentally with, but not as a result of, the damage to the liver, because we do not see such megaloblastic anemia associated with cirrhosis of the liver in China, where pernicious anemia is exceedingly rare¹³ and the anemia associated with the cirrhosis occurs in its uncomplicated form The other instances of macrocytic anemia associated with cirrhosis are the result of hyperplasia of the bone marrow, as exhibited in our 2 cases The cause for such hyperplastic erythropoiesis is not yet known Heinle and others¹⁴ stated the belief that increased destruction of blood may play a role in the anemia of liver cirrhosis, and Tsai and his associates¹⁵ showed that congestion of the spleen causes increased fragility of the red cells

In all cases of cirrhosis of the liver, the spleen is continuously much congested, it would be logical to conclude that anemia associated with cirrhosis is probably due to increased destruction of blood in the much congested spleen, which process perhaps does result in the majority of cases of normocytic and normochromic anemia In a small percentage, however, in which the destruction is much exaggerated and the demand on the bone marrow is naturally intensified, the marrow may become hyperplastic and produce the large cells to make the anemia macrocytic A correlation between the degree of macrocytosis and the size of the spleen would be of interest

Our observation may explain the apparent discrepancy between the report by Goldhamer and his associates³ on a case of cirrhosis of the liver associated with macrocytic anemia, in which the liver was proved to contain no hemopoietic principle, and a report by Schiff and his

12 Wintrobe, 7^d, p 318

13 One of us (K-w H) has seen only 1 patient with typical megaloblastic anemia during eight years' clinical experience in Chengtu Snapper, I Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941, p 264

14 Heinle, R W, Gastle, W B, and Rose, F A *Folia haemat* 64 174, 1940

15 Tsai, C, Lee, J S, and Wu, H *Chinese J Physiol* 15 165, 1940

associates⁴ on cases of hepatic disease, in which the liver was proved to have stored the principle satisfactorily. No doubt, the case of Goldhamer and his co-workers was one of cirrhosis complicated by pernicious anemia in relapse, and the liver, of course, contained no such principle, whereas the cases of Schiff and his associates were probably uncomplicated examples of hepatic diseases, in which the liver, as in our 32 cases, did not fail to store the principle.

Therefore, one may conclude that damage to the liver, as in cirrhosis, probably does not interfere with the function of storage of the hemopoietic principle or with the final stage of its synthesis, because it does not give rise to megaloblastic anemia and because the liver has been proved to have stored the principle satisfactorily.⁴ Anemia occurring with cirrhosis of the liver is of the normocytic type in the majority of cases, but occasionally it is macrocytic, of the hyperplastic type. The mechanism is not clear, but stasis of a great amount of blood in the enlarged spleen may cause increased destruction of blood and thereby may bring about a normocytic anemia, when the process is intensified, hyperplasia of the bone marrow may result in macrocytosis.

SUMMARY AND CONCLUSION

Thirty-two cases of cirrhosis of the liver associated with anemia were studied hematologically. The anemia in all cases was found to be normocytic except in 2, in both of which it was macrocytic, in 1 of which the presence of the so-called hyperplastic normoblasts was established in the marrow and in none of which megaloblastic erythropoiesis was observed.

The pathogenesis of macrocytosis associated with cirrhosis of the liver is discussed.

Chronic damage to the liver as it occurs in cirrhosis probably does not interfere with the proper storage of the hemopoietic principle or with the final stage of its synthesis and therefore does not give rise to megaloblastic anemia.

DEVELOPMENT OF PORPHYRIA IN DIABETES MELLITUS

Report of Three Cases

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SINCE Gunther's original description of acute porphyria as a clinical entity was published in 1911, a number of reviews¹ have appeared on the subject. Although porphyria and porphyrinuria have been associated with many toxic states and with other disease entities,^{1a,f} the only reference in the literature to an association of acute porphyria with diabetes mellitus seems to be the statement, "it has also been found in diabetes mellitus," appearing in the section on porphyria in Duncan's textbook²

At the Albert Merritt Billings Hospital there are, at the time of this report, records of a total of 8 proved cases of acute porphyria, in 3 of which the diagnosis of diabetes mellitus was also substantiated. In each case, the diabetes had been present for some years before symptoms of porphyria appeared.

The apparently complete dissociation of pigment metabolism and carbohydrate metabolism makes it difficult to suggest an explanation for the curious concomitance of these two metabolic disorders.

From the Frank Billings Medical Clinic, University of Chicago, The School of Medicine

1 (a) Dobriner, K, and Rhoads, C P. The Porphyrins in Health and Disease, *Physiol Rev* **20** 416-468, 1940. (b) Mason, V R, Courville, C, and Ziskind, E. Porphyrins in Human Disease, *Medicine* **12** 355-439, 1933. (c) Nesbitt, S, and Watkins, C H. Acute Porphyria, *Am J M Sc* **203** 74-83, 1942. (d) Waldenstrom, J. Some Observations on Acute Porphyria and Other Conditions with a Change in the Excretion of Porphyrins, *Acta med Scandinav* **83** 281-316, 1934. (e) Studien uber Porphyria, *ibid*, 1937, supp 82, pp 1-254. (f) Watson, C J. The Porphyrins and Their Relation to Disease, in Christian, H A, and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1921, vol 4, pt 2, p 228.

2 Duncan, G G. *Diseases of Metabolism*, ed 2, Philadelphia, W B Saunders Company, 1947.

REPORT OF CASES

CASE 1—*First Admission*—M G, a man, married, a real estate agent aged 34, on entering the hospital had had paralysis of the arms and legs for two months

History Three years before admission the patient had noted the onset of weakness and fatigue, with a loss of weight of 60 pounds (27 Kg) in three months. A physician found complete reduction of copper in the urine and diagnosed diabetes mellitus. There had been no polydipsia, polyuria or polyphagia. After four months' trial on a diet the patient was given protamine zinc insulin, 30 to 35 units daily. Glycosuria was fairly well controlled, and the patient was normally active. The patient's father was known to have had diabetes for ten years, but there was no other family history of the disease.

Four months before admission the patient took a long bus trip during which insulin was omitted for two days. He became ill and was admitted to a hospital in acidosis, which was treated with fluids intravenously and large amounts of insulin. During his stay, paraldehyde sedation was given. In a week he was discharged as improved.

On his return home his wife, who tested his urine, noted a reddish coloration of the urine which was almost continuous, though varying in degree. After three days at home severe weakness, headache, nausea and vomiting developed and the patient was readmitted in coma, in which state he was said to have remained for several days in spite of the administration of large amounts of insulin. Subsequently the level of blood glucose was said to have dropped abruptly to 27 mg per hundred cubic centimeters, at which time the patient's legs and arms felt numb and he was almost unable to move them, although he retained good strength in the fingers and toes. There was aphonia, but at times he could speak in a faint whisper. For several days he was incontinent in feces and urine. Examination of the spinal fluid showed only a positive response to the Pandy test. The patient was discharged but bedridden after six weeks, subsequently recovering enough motor power to sit up sometimes, but during the eight weeks before the first admission to the Albert Merritt Billings Hospital he was too weak to clear the mucus from his mouth and he complained of needle-like pains in the extremities. For two weeks he had nausea, vomiting, diarrhea and chills, and during the four days prior to admission he was again incontinent of feces.

During the ten years prior to admission there had been exposure to lead paint when the patient worked as a building supervisor.

Physical Examination The temperature was 98 F and the pulse rate 130, and there were 28 respirations per minute. The patient was an emaciated young adult man, unable to move his extremities, appearing acutely ill and breathing rapidly. He could not speak or swallow and had no control over the sphincters of the bladder or rectum. The ophthalmoscopic examination was noncontributory. The skin was warm and moist. There was dulness over the lung bases with many moist rales. The heart was not enlarged, but the rate was rapid and the sounds were distant. The pulse was weak. The blood pressure was 90 systolic and 50 diastolic. The edge of the liver and the tip of the spleen were felt on deep inspiration. The genitalia were normal, and the rectal examination was noncontributory. There was some edema of the dorsal surfaces of the feet. The extremities were markedly wasted and showed flaccid paralysis, with weak hand grasp and absence of reflexes. The vibratory sense was absent. A pinprick was discerned only as a "numb" feeling over the extremities.

Laboratory Examination The urine was often dark reddish brown and gave a positive response to the test with Ehrlich's aldehyde reagent in dilutions as high as 1:256. The specific gravity ranged up to 1.025. Glycosuria was usually

minimal but sometimes severe, and there was occasional acetonuria. A twenty-four hour specimen of the urine contained 0.011 mg of lead. There were many white blood cells, and *Aerobacter aerogenes* was cultured, both the pyuria and the bacteriuria cleared after sulfonamide therapy. Hematologic examinations gave normal results except for leukocytosis of 28,000 to 32,000 cells per cubic millimeter, with 86 per cent polymorphonuclear leukocytes, the leukocyte count was subsequently 12,000 to 15,000. The basal metabolic rate was minus 5. Roentgenograms of the chest and gallbladder were normal. Three examinations of the spinal fluid were noncontributory. The stools showed occasional occult blood. The values for blood sugar were occasionally above 200 mg per hundred cubic centimeters, once reaching 364 mg and a few times falling to hypoglycemic levels. The levels for serum carbon dioxide and chlorides were normal, as was the pH , and the level for cholesterol was 210 mg per hundred cubic centimeters. The concentration of plasma proteins was 6.40 Gm per hundred cubic centimeters, with hypoalbuminemia (3.26 Gm) and hyperglobulinemia (3.14 Gm).

Course. This first admission, of ten months' duration, was marked by irrationality, abdominal pain, insulin reactions and convulsions in the earlier weeks and, subsequently, gradual improvement of the peripheral neuritis to a point where the patient could walk with a "walker." There was frequent paresthesia of the limbs. During more than half his stay the patient had a low grade intermittent fever with moderate leukocytosis, later this diminished somewhat. He exhibited periods of unresponsiveness and had bizarre hallucinations and delusions such as "awaking in a pool of blood," "having a brain in my back," etc. The diabetes was difficult to manage. Alimentation proved a major problem, requiring tube feeding for long periods. As the neurologic condition improved, the diabetes was controlled fairly well with 30 units of protamine zinc insulin and 15 units of crystalline zinc insulin each morning and 5 units of crystalline zinc insulin before supper. There were a number of episodes of agonizing abdominal pain, and toward the middle of this admission, prior to the identification of porphyrins in the urine, the patient underwent laparotomy and appendectomy during which extreme hypermotility of the ileum and colon was observed.

Excess urinary porphyrins were demonstrated by red fluorescence in ultraviolet light after ether extraction of the urine and confirmed by spectroscopic examination. After porphyrins were found in the urine, barbiturates were withheld. The patient received brewers' yeast, wheat germ oil, vitamin B preparations and injections of crude liver extract solution® and was treated by physical therapy. In the ensuing months, marked clinical improvement occurred, with a gain in strength, increased rationality and cessation of the abdominal pain. After discharge, the patient's motor power improved with the same regimen and he continued physical therapy at home, where he walked with crutches.

Second Admission.—On readmission a year later, the patient was ambulatory with help. He had generalized muscular weakness and atrophy, most pronounced at the distal joints (especially of the legs) but much less severe than before. The biceps and triceps reflexes were fairly active, the patellar reflexes weak and the ankle jerks absent. Sensation was normal in the arms, but there was a distal stocking hypalgesia and hypesthesia, with absence of the vibratory sense in the ankles. Porphyrins were again demonstrated in the urine, and the patient had another attack of acute abdominal pain. After discharge he had a "right-sided convulsion," after which the right arm and leg became weaker than the left and he fed himself with the left hand. There was a recurrence of progressive weakness, and there were episodes of agonizing pain in the abdomen and back.

Third Admission—The patient was admitted for the third time two years after the first entry, with flaccid quadriparesis, distal paralysis, areflexia and hyperalgesia over the feet and legs and hypalgesia over the hands. There were irrationality, delusions and hallucinations, including "having four eyes," seeing the late President Roosevelt in the room, etc. Again porphyrins were demonstrated in the urine. Subsequently there was again improvement in motor power, and eventually the patient became able to walk without help. For two years, during which he was not followed, there was no redness of the urine or abdominal pain.

Fourth Admission—The patient's final admission, for what was thought to be tuberculosis with cavitation of the upper lobe of the right lung, was preceded by six months of cough and hemoptysis during which time he did not seek medical attention. Previous roentgenograms had shown the chest normal. Pneumothorax, performed elsewhere, had not achieved satisfactory collapse and there was subsequent rupture of an adhesion, with hydropneumothorax, followed by empyema with hemolytic *Staphylococcus aureus*. Fluid of a dirty brown color reaccumulated after numerous thoracenteses. Tubercle bacilli were never demonstrated in the sputum or the pleural fluid. Terminally, oliguria occurred and the diabetes was out of control. The level of blood urea nitrogen rose to 59 mg per hundred cubic centimeters. The level of serum phosphorus was 7.3 mg per hundred cubic centimeters and that of serum calcium 7.2 mg. The patient died during a clonic convulsion. During this admission, porphyrins and porphobilinogen were intermittently present in the urine.

Diagnoses—A clinical diagnosis of porphyria and diabetes mellitus was made, and the following conditions were diagnosed at autopsy: pyopneumothorax of the right side with chronic interstitial pneumonitis, massive atelectasis of the right lung, compensatory emphysema of the left lung, chronic fibrous pleuritis of the right side, fine fibrous adhesions of the left apical region, ulcerative esophagitis, mild chronic pyelonephritis, decubitus ulcers in the left gluteal region and absence of the appendix.

Chemical Study—The study (by Dr. H. Kluver) of various organs, tissues and body fluids revealed large amounts of various ether-soluble and ether-insoluble porphyrins, partly in the form of the zinc complex. Further details will appear in another paper.

CASE 2—H. S., a white man, an executive aged 53, with diabetes mellitus of five years' duration, entered the hospital with the complaints of anorexia, loss of weight and dyspnea.

History—The diabetes had been regulated by diet alone until five months before admission when, because of a fasting blood sugar level of 150 mg per hundred cubic centimeters, the patient had been given 30 units of protamine zinc insulin each morning. This was discontinued seven weeks later because of lower blood sugar levels. Four months before admission, after having had several teeth extracted and having been given poorly fitting dentures, the patient had experienced the onset of loss of appetite, weakness and moderate exertional dyspnea, all progressive up to the time of admission and accompanied by a 60 pound (27 Kg) loss of weight. Two weeks before admission he noted increased prominence of the veins of the forehead and intermittent darkness of the urine. There was no edema of the ankles and no abdominal pain. He had been taking pentobarbital sodium (nembutal®) each night and at the time of admission was taking 3 grains (0.19 Gm) of seconal sodium® each night because of insomnia. The past history was significant in that he had had syphilis at 16, the disease was treated with "hip shots" for three years, at which time the response to serologic tests became

negative Tests of the blood and spinal fluid since the termination of treatment had been consistently normal Five years before admission, during exercise, the patient had been seized with severe precordial pain that radiated to the left arm and persisted, gradually diminishing in severity, until the following morning Two years before admission, while the patient was hospitalized elsewhere for weight reduction, a sudden severe pain developed in his neck An electrocardiogram at that time was said to have revealed a myocardial infarction, and he spent the subsequent six weeks in bed There was no history of angina pectoris The family history revealed that the patient's mother had died at 59 of diabetes mellitus and nephritis, 3 sisters had died of cancer and 1 brother had disease of the coronary arteries

Physical Examination—The temperature was 36.2 C (97.2 F), the pulse rate was 100 and there were 20 respirations per minute The patient was a gray-haired, middle-aged man with evidence of marked recent weight loss, appearing chronically ill but in no acute distress There were 4 teeth remaining The chest was emphysematous in form A few inspiratory rales were heard at the base of the lungs The heart was slightly enlarged to the left, with a gallop rhythm The blood pressure was 150 systolic and 90 diastolic The liver was palpable in the right upper quadrant, but the edge was not clearly felt The neurologic examination was normal Numerous small subcutaneous nodules were palpable over the abdominal wall The circulation times were prolonged. Proctoscopy was noncontributory

Laboratory Examination—On the patient's admission the hemoglobin concentration was 16.5 Gm per hundred cubic centimeters, the red cell count was 5,500,000, and the white cell count, 12,650 The urine was orange-red in color, having a specific gravity of 1.034, a 1 plus value for albumin, no reduction of Benedict's solution, no acetone and a 2 plus reaction to Ehrlich's test for urobilinogen Subsequently the test for porphobilinogen by the aldehyde reaction was positive, hence, it was assumed that porphobilinogen was mistaken for urobilinogen The reaction to the Kahn test for syphilis was negative on two occasions Specimens of the stools were negative for occult blood The basal metabolic rates were minus 19 and minus 5 A gastric analysis revealed free acid after the administration of histamine Roentgenographic studies showed a normal gallbladder, esophagus, stomach, duodenum and colon A roentgenogram of the chest revealed an enlarged heart (70 per cent oversize) and moderate basilar pulmonary congestion An electrocardiogram showed strain of the left ventricle and an intraventricular conduction defect Chemical studies of the blood showed the following values: glucose concentration, 135 to 203 mg per hundred cubic centimeters, nonprotein nitrogen, 25 mg, serum carbon dioxide, 31.7 millimols per liter, serum pH , 7.41, serum chlorides, 101 milliequivalents, serum cholesterol, 335 mg, and esters, 253 mg, alkaline phosphatase, 5.1 Bodansky units, serum bilirubin, 0.3 mg (direct), and 0.5 mg (total), and total plasma proteins, 6.42 Gm (albumin, 4.04 Gm, and globulin, 2.38 Gm) The reaction to the thymol flocculation test was negative, and the value for cephalin flocculation was 1 plus The value for the urea clearance test of Van Slyke was 54 cc per minute, using the square root formula

Course—Throughout the patient's twenty-three day hospital stay, glycosuria was minimal or absent on a 1,650 calorie diet with 150 Gm of carbohydrate and no insulin Because of the persistence of symptoms involving the chest, the patient was digitalized beginning on the nineteenth hospital day He complained bitterly of insomnia, for which he received various combinations of pentobarbital sodium, phenobarbital and amobarbital sodium (amytal sodium®) for the first fifteen days

Fair sedation was eventually obtained with a combination of whisky and chloral hydrate. Increased salivation was a prominent symptom. The urine remained persistently a dark orange to an orange-red color. On several occasions it was found by the aldehyde test^{1e} to contain porphobilinogen. Exposure to ultraviolet rays after ether extraction indicated excess porphyrins on one occasion. At no time did the patient complain of abdominal pain. No neurologic abnormalities were demonstrated, and no psychotic behavior occurred. He had three to five bowel movements each day.

After discharge, the patient was followed in the outpatient clinic for six months, after which he did not return. During that time, his urine remained dark in color. On one occasion he was thought to show peculiar behavior. He continued to have three to five bowel movements each day, and severe insomnia persisted in spite of the reinstitution of barbiturates.

Final Impression—The final impression was that this was a case of porphyria, diabetes mellitus and arteriosclerotic heart disease.

CASE 3—First Admission—S. A., a housewife of 57, entered with pain and tenderness of two years' duration in the right upper quadrant of the abdomen and the right lower portion of the chest and complaining of a ten day exacerbation with intractable vomiting.

History The patient had considerable difficulty with the language, which made the taking of a history unsatisfactory. She had been known to have diabetes for twenty years, the condition had been satisfactorily controlled with 10 units of protamine zinc insulin daily. Twenty years previously she had had gonococcal inflammatory disease of the pelvis and had undergone a pelvic operation. Approximately ten years previously she had had empyema of the right side, which had been treated by aspiration. Three years before her admission to this hospital an emergency operation had been performed for a strangulated hernia of the right femoral canal.

The patient's chief complaint dated back two years before admission, when she noted the onset of episodes of pain in the right upper quadrant of the abdomen, in the right lower portion of the chest and in the back, sometimes associated with vomiting. At times she suffered pain in the right shoulder, with or without radiation down the right arm. The latter pains sometimes occurred independently, and at other times in association with the pain in the right upper quadrant and in the right lower portion of the chest. The patient had had one or more episodes of cystitis, during which she was treated by her physician. Two months before this admission the pains in the right lower portion of the chest and in the abdomen became increasingly severe, with nausea and vomiting, and she entered another hospital. Roentgenograms of the gallbladder and retrograde pyelograms were normal. A neurologic consultant considered the pain "hysterical" in origin. After discharge the patient was no better and continued to have similar episodes. Ten days before admission to the Albert Merritt Billings Hospital there was exacerbation of the pain with paroxysms of vomiting and nausea. The pain apparently was worse and more frequent after meals, and the patient vomited all solid foods. In the clinic and on admission there was acetone in the urine, with only minimal glucose or none.

Physical Examination The temperature was 36.6 C (97.9 F), the pulse rate was 88 and there were 20 respirations per minute. The patient was a well developed, fairly well nourished, elderly white woman who appeared depressed and rather chronically ill. She was restless, complaining of the pain as has been indicated. The skin and lymph nodes were normal. An ophthalmoscopic

examination showed a widened arteriolar light reflex, tortuosity of the arterioles and arteriovenous compression with scattered punctate hemorrhages and small, white, circumscribed exudates. The head, ears, nose, mouth, neck, breasts, chest and heart were not remarkable. The blood pressure was 120 systolic and 78 diastolic. Examination of the abdomen revealed pronounced tenderness in the right upper quadrant even on gentle palpation,³ and there was tenderness over the right lower portion of the chest and at the right costovertebral angle. The edge of the liver was felt 1 to 2 fingerbreadths below the right costal margin on inspiration. There were incisional scars on the right thigh and in the right suprapubic region. A neurologic examination was noncontributory.

Laboratory Examination On admission of the patient the urine reduced Benedict's solution (1 plus) and contained acetone (1 plus). Later the same day there was no sugar but the acetone reaction was 4 plus. (During the latter part of the patient's course the glycosuria varied from 0 to 1 or 2 plus.) The urine was normal in color at all times. The aldehyde test³ showed no porphobilinogen, but further tests for porphyrins were not carried out during this admission. Microscopic examinations of the sediment during the first days of the patient's stay revealed 15 to 50 white blood cells per high power field. *Escherichia coli* was cultured on two occasions, the infection cleared on sulfadiazine therapy. Hematologic examinations, the Kahn test and examinations of the stools gave normal results. A gastric analysis showed no free acid in the fasting specimen and 54 units of free acid fifty minutes after the administration of histamine. Tests of liver function gave normal results. Blood sugar was occasionally above 200 mg per hundred cubic centimeters. Roentgenograms revealed the gallbladder, stomach, small intestine, colon and renal pelves to be normal. Splenic calcifications were observed. A roentgenogram of the chest showed nothing remarkable except calcification in the aortic arch and the major bronchi, there were minimal osteoarthritic changes in the thoracic portion of the spine. Fluoroscopic examination of the chest showed adequate motion of the diaphragm. Electrocardiograms disclosed right axis deviation with a prolonged QRS complex (0.12 seconds) and deep Q waves in leads II and III, interpreted on serial tracings as indicating a high grade intraventricular conduction defect and possible infarction of the posterior portion of the myocardium.

Course The starvation ketosis present on the day of admission was promptly remedied by hypodermoclyses of dextrose and isotonic sodium chloride solution. The diabetes was satisfactorily controlled with globin insulin with zinc (20 units daily). The pains continued, occurring sometimes at irregular intervals but often after meals, which made feeding somewhat difficult. Toward the latter part of the patient's thirty-one day stay in the hospital, she felt somewhat better and was discharged, being able to take food well and to walk haltingly.

On her return home she did well for a week, although the pain persisted. It then became much severer, radiating up into the right side of the chest and the right shoulder almost constantly in the last three days before the second admission, at which time there were repeated emeses. She was brought back to the hospital agitated, making facial grimaces and drooling foamy saliva.

Second Admission—During this admission the patient exhibited considerable fluctuation in the severity of the pain, which sometimes seemed to be relieved with sterile hypodermic injections. For a while there was hemihyperalgesia of the entire right side, but no other abnormal neurologic signs were observed.

3 Watson, C. J., and Schwartz, S. A Simple Test for Urinary Porphobilinogen, *Proc Soc Exper Biol & Med* 47:393-394, 1941.

At the beginning of the third week large amounts of porphyrins were found in the urine by exposure to ultraviolet light and spectroscopic examination after extraction with ether and acetic acid⁴. The urine remained normal in color, however, even when left exposed to sunlight for two weeks. Despite the presence of porphyrins, the aldehyde test³ showed no porphobilinogen in the urine at any time. Subsequently all barbiturates were withheld without evident change in the clinical course.

At the end of the third week the patient had a brief episode of panic in which she left the bed and wandered down the corridor. When found she was cyanotic and was grimacing and blowing through her teeth. She expressed paranoid ideas, thinking that one of the interns was trying to kill her and that she had telephoned her husband. On her being put back to bed, the cyanosis subsided. Thereafter she had no similar episodes but retained her ideas about the imagined events.

During the third week there were dyspnea, tachycardia and basilar pulmonary rales and the liver was enlarged 8 cm below the right costal margin. The patient gained weight progressively. A roentgenogram of the chest showed a small pleural effusion and increased bronchovascular markings. Considerable improvement followed digitalization, the intravenous administration of mercuraphylline injection (mercuzanthin®) and aminophylline and the administration of ammonium chloride and a salt-poor diet. There was diuresis with a loss of 5 Kg of body weight. Subsequently there was considerable improvement in the patient's general appearance with less frequent emeses, though she still complained of constant pain in the right portion of the thorax and in the right upper quadrant of the abdomen. The diabetes was finally controlled with 20 units of protamine zinc insulin and 5 units of crystalline zinc insulin every morning. While the patient had maximal pains her insulin requirement was higher (up to 30 units of protamine zinc insulin and 10 units of crystalline zinc insulin). During days of severe pain, twenty-four hour urine specimens contained up to 37 Gm of glucose.

When the patient's condition appeared stable, she was discharged and went home to the care of her private physician. During the succeeding four months the patient was followed in the clinic. She continued to complain of abdominal pain in the right upper quadrant, especially after eating, and there were frequent rather severe attacks with facial grimacing and crying out. Triple bromide tablets and glyceryl trinitrate were said to have afforded some relief. There was occasional nocturnal dyspnea.

Third Admission—Three days before the third admission the patient fell down at home, striking her head. There was a small amount of bleeding from the scalp. The pain became worse. She was confused, had dizzy spells, was unable to stand, complained of dyspnea and was admitted as an emergency patient.

The examination showed swelling over the right parietal region but no evidence of laceration or fracture. On this occasion the lungs were clear and the heart was not enlarged to percussion, but there was now a harsh apical systolic murmur transmitted to the left axillary region. The liver was felt 2 fingerbreadths below the right costal margin. There was tenderness to a light touch all over the abdomen.

As on the second admission, urinary porphyrins were demonstrated by fluorescence in ultraviolet light after extraction with ether and acetic acid, but they were present in smaller amounts than previously. The urine was again of normal color and no porphobilinogen was demonstrated by the aldehyde test.

4 de Langen, C. D., and ten Berg, J. A. Porphyrin in the Urine as a First Symptom of Lead Poisoning, *Acta med Scandinav* 130 37-44, 1948.

The serum bromide level was 219 mg per hundred cubic centimeters, and sodium chloride was given

After initial improvement in the patient's mental state, she suddenly became weak on the evening of the third day. The extremities were cold, the pulse was faint and the blood pressure was unobtainable. The urine showed a small amount of glucose. She was given 25 Gm of glucose intravenously without effect. An electrocardiogram was unsatisfactory because of twitching movements as the patient lapsed into coma, but Wenckebach's periods were discernible in lead I. After brief tonic and clonic convulsions the heart sounds became irregular and the patient died.

Diagnoses—Porphyria and diabetes mellitus were the clinical diagnoses. The following were determined at autopsy: extreme arteriosclerosis of all organic arteries, especially the coronary arteries, old occlusion of the right coronary artery and healed infarction of the posterior portion of the left ventricle, arteriosclerotic obliteration of the coronary arteries, recent occlusion of the left coronary artery at its bifurcation and infarction of the entire (?) left ventricle, pulmonary edema and hyperemia, hydrothorax of the left side and fibrous obliteration of the right pleural space, arteriosclerotic atrophy of the brain, arteriosclerotic scarring of the cortex of the kidneys, atrophy of the tail of the pancreas and hyalinization of the islets of Langerhans, fatty infiltration of the liver, acute splenic hyperplasia (cause undetermined), recent superficial occipital contusion, and chronic endocervicitis and absence of the ovaries, the fallopian tubes and the body of the uterus (a healed surgical incision was noted).

COMMENT

In all 3 cases here reported, diabetes antedated the first symptoms or observations suggesting the presence of porphyria.

The first patient had diabetes of three years' standing before the sudden onset of porphyria, characterized by generalized paresis and dark-colored urine. At the time of onset the patient was hospitalized elsewhere for the treatment of acidosis, it is known that he received large amounts of insulin and was at one time in severe hypoglycemia. He was said to have received large amounts of paraldehyde. Whether barbiturates or sulfonamide drugs were administered at that time could not be determined, but under our observation the withdrawal of all barbiturates was followed by rather pronounced clinical improvement. The patient was, however, receiving large doses of crude liver extract solution⁵ as well as other medicaments during that time. The patient had had contact with lead paints over a period of several years, although not immediately preceding the onset of paresis. Since the urinary excretion of lead was found to be well within normal limits,⁵ plumbism as a cause of the porphyrinuria⁶ in this case can be discounted. Prior to the diagnosis of porphyria, the possibility of diabetic polyneuritis had

5 Goodman, L., and Gilman, A. *The Pharmacological Basis of Therapeutics*. A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941, p. 723.

6 de Langen and ten Berg.⁴ Waldenstrom.^{1d}

been considered by some of the physicians who saw the patient. It is worthy of note that at laparotomy extreme intestinal hyperperistalsis was observed. (Gastric atony and diminished peristaltic sounds were described by Berg,⁷ whereas severe gastrointestinal spasm was described by Prunty⁸.)

The second patient had had diabetes for five years before the passage of dark urine was noted. The prolonged use of barbiturates preceded the onset of porphyrinuria in this case. Excess urinary excretion of porphyrins was repeatedly demonstrated, but none of the usual clinical manifestations of acute porphyria was observed except intractable insomnia.

In case 3, the patient had had diabetes for twenty years before the onset of abdominal pain. As the psychic and neurologic manifestations became more severe, a steady rise in the insulin requirement took place in spite of diminished carbohydrate intake.

In none of the cases were quantitative studies or qualitative extraction with identification of specific porphyrins, as described in the literature,⁹ carried out. In all three instances, excessive quantities of porphyrins were demonstrated by ether extraction, but this fraction was certainly only a small part of the total colorless porphyrins present. In cases 1 and 3 the identification of the ether extract as a porphyrin mixture was not only shown by fluorescence in ultraviolet light but also confirmed by spectroscopic examination. In cases 1 and 2 the urine was often deep orange to red in color with increased intensity on exposure to light and when colored consistently gave a positive reaction to the aldehyde test with production of a chloroform-insoluble pigment, presumably porphobilinogen.³ The third patient had urine of normal color with large amounts of colorless porphyrins, but it did not contain the reddish brown porphobilin or its precursor porphobilinogen or other pigments commonly found in acute porphyria.¹⁰ In no case was the porphyrin content of the feces determined.

According to the classification set forth by Mason and his co-workers^{1b} all these cases fall into the category of acute porphyria, but whether there is sufficient evidence to implicate a single toxic factor in any of the cases is open to question. There was no definite family history of symptoms of porphyria in any of the 3 cases, whereas in cases 1 and 2 there were family histories of diabetes.

7 Berg, M. Acute Porphyria. Clinical and Pathologic Observations, *Arch Int Med* **76** 335-340 (Nov-Dec) 1945.

8 Prunty, F. T. G. Acute Porphyria, *Arch Int Med* **77** 623-642 (June) 1946.

9 Dobriner and Rhoads^{1a} Watson^{1f} Prunty⁸

10. Nesbitt and Watkins^{1c} Goodman and Gilman⁵

The cases here reported are too few to support a hypothesis that diabetes mellitus and porphyria are causally related. Further light may be shed on this question by the performance of glucose tolerance tests in patients with porphyria and by urinary porphyrin studies in patients with diabetes, especially those thought to have "diabetic polyneuritis."

In the early stages the differentiation of porphyria and diabetic neuritis may be difficult inasmuch as both may involve aching pains in the limbs, muscular tenderness, hyperesthesia and various types of paresthesia, weakness, muscular atrophy, diminution or absence of tendon reflexes and loss of various sensory modalities, including vibration sense, demonstrable by objective tests¹¹. The arms, the legs or the trunk may be most affected in porphyria, whereas diabetic polyneuritis usually involves primarily the lower extremities. In some cases of porphyria the proximal (girdle) musculature of the hips and shoulders is predominantly affected, as may be the case in the Guillain-Barré syndrome but not ordinarily in other neuritides. The diagnosis of porphyria is favored by the occurrence of severe abdominal pains simulating those of an acute surgical condition of the abdomen, with radiation to the lumbar, sacral or femoral regions, and by the dramatic and bizarre manifestations of excitement, delirium, hallucinations and convulsions. Inspection of the urine and examination for porphobilinogen and porphyrins may elucidate some otherwise baffling diagnostic problems.

SUMMARY

Three cases with concomitance of diabetes mellitus and porphyria among a total of 8 cases of porphyria recorded at the Albert Merritt Billings Hospital are described. In each instance, diabetes preceded the onset of symptoms of porphyria.

It is suggested that glucose tolerance tests be performed in cases of porphyria and that urinary porphyrins be sought in cases of diabetes, especially those in which the condition is thought to be "diabetic polyneuritis."

¹¹ Brain, W. R. *Diseases of the Nervous System*, ed. 2, London, Oxford University Press, 1940. Wilson, S. A. K. *Neurology*, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940.

MULTIPLE MYELOMA WITH NEW BONE FORMATION

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THERE is unanimity of opinion among authorities on the subject that the typical and characteristic lesion of bone in multiple myeloma is a discrete osteolytic involvement. The roentgenographic appearance is usually that of a punched-out area with sharp margination and without evidence of surrounding productive reaction. In a description of multiple myeloma Boyd¹ stated, "It is a pure rarefying lesion with no formation of new bone." To quote Geschichter² "The widespread occurrence of small, sharply demarcated defects in the marrow cavity, unaccompanied by bending deformity or the formation of new bone, are the cardinal features in the diagnosis of multiple myeloma." Snapper³ affirmed that in multiple myeloma "no new formation of bone takes place." Shanks, Kerley and Twining⁴ declared categorically concerning the osseous lesions of multiple myeloma that "they are entirely osteolytic, and never give rise to new bone formation."

The case to be presented is of unusual interest because it has been possible to demonstrate conclusively by histologic and roentgenographic study the formation of new bone in a patient with proved multiple myeloma. A search of the literature of this disease has brought to light no other case in which a significant degree of new bone formation, aside from that occurring at the site of pathologic fracture, was visualized on histologic and roentgenographic examination.

From the Medical Service, Dr S Biloon, Director, Dr William Aronson, Pathologist, and Dr Samuel Weitzner, Radiologist, Morrisania City Hospital.

1 Boyd, W. A Text-Book of Pathology. An Introduction to Medicine, Philadelphia, Lea & Febiger, 1934, p 968.

2 Geschichter, C, in Pillmore, G. Clinical Radiology. A Correlation of Clinical and Roentgenological Findings, Philadelphia, F A Davis Company, 1946, vol 2, p 614.

3 Snapper, I. Medical Clinics on Bone Diseases. A Text and Atlas, New York, Interscience Publishers, Inc, 1943, p 36.

4 Shanks, S C, Kerley, P, and Twining, E W. A Text-Book of X-Ray Diagnosis, London, H K Lewis & Co, Ltd, 1939, vol 3, p 630.

REPORT OF A CASE

History—P K, a 68 year old white woman, was admitted to Morrisania City Hospital on Jan 3, 1949 for the first time. She had been well until six months prior to entry, when she had begun to complain of mild but steady headache. About four months later her right eye began to swell, and insidious weakness of the left arm, and subsequently of the left leg, was noted. She complained of double vision. She was then taken to an oculist, who, in turn, referred her to a neurologist. The latter made a diagnosis of cerebral thrombosis. The patient continued up and about until ten days before admission, at which time she became totally bedridden. Anorexia had developed, and she had lapsed into semistupor. There was no definite weight loss, no melena and no vaginal discharge or bleeding. The patient, however, had vomited occasionally since the onset of her illness. Concomitant with the

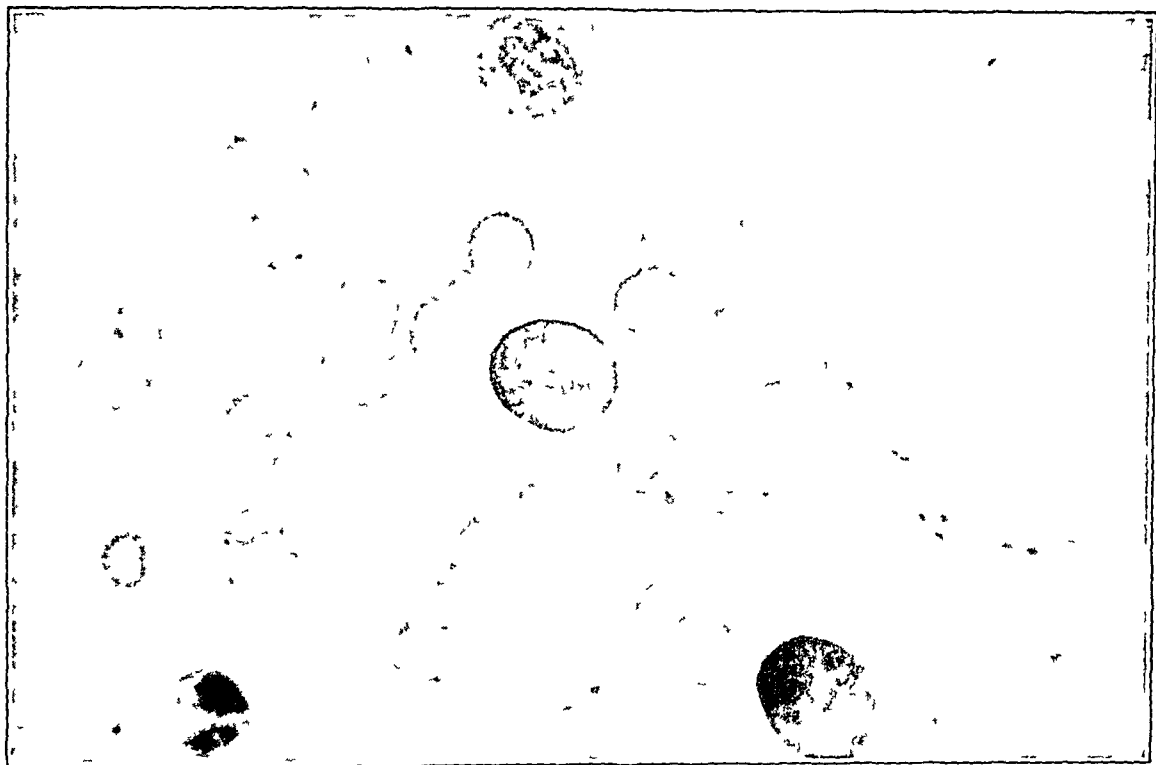


Fig 1—Smear of peripheral blood showing plasma cells. At one examination 70 per cent of the leukocytes were comprised of these cells.

ocular disturbances appeared several soft swellings on her forehead, not associated with any trauma.

Examination—The patient was an elderly white woman lying quietly in bed, semicomatose but able to be aroused by painful stimuli, unable to speak and apparently unable to understand speech. Her blood pressure was 120 systolic and 60 diastolic, her pulse rate 80 per minute and her temperature 98.6 F. On her forehead were several soft, resilient, cystic, walnut-sized swellings. On palpation these were found to overlie actual circular defects in the frontal bone. Examination of the eyes disclosed the right eye to be proptosed and immobile. The pupil was dilated and did not react to light. The left eye was normal. Both fundi revealed blurred disks. Examination of the heart, lungs and abdomen revealed no abnormalities. There was no adenopathy, no splenomegaly and no hepatomegaly. Neurologic examination disclosed a definite hemiparesis on the left. The patient was seen by the neurologic consultant, whose opinion it was that she had a lesion of the mid-



Fig 2—Smear of sternal marrow The bone marrow is characteristic of extremely malignant multiple myeloma

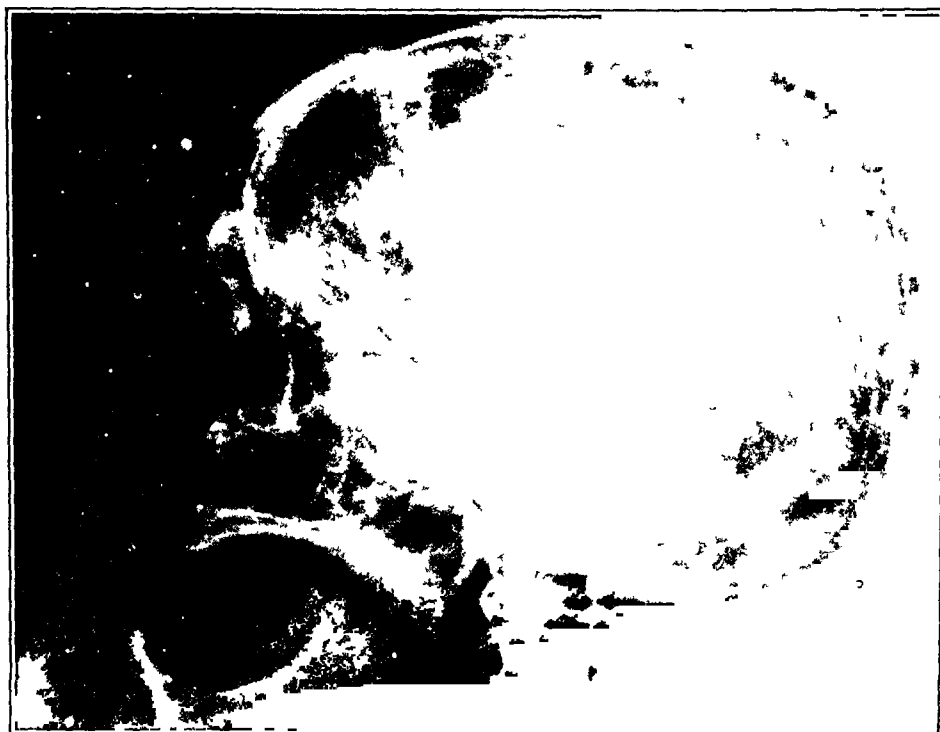


Fig 3—Extensive area of destruction in the frontal bone There is a great number of small punched-out areas

brain due to metastatic brain disease. A spinal tap was performed. The initial pressure was 150 mm of water. All cytologic, chemical and serologic observations were within normal limits.

Laboratory Data—Routine urinalysis revealed no abnormalities. The total protein content of the blood was 7.8 Gm per hundred cubic centimeters (albumin 4.2 Gm and globulin 3.6 Gm). The albumin-globulin ratio was 1.2:1. The serum cholesterol level was 326 mg per hundred cubic centimeters, cholesterol esters, 97 mg, acid phosphatase, 2.3 Gutman units, alkaline phosphatase, 10.4 King-



Fig. 4—Diffuse productive process involving the entire shaft of the left humerus. Dense bony spicules are arranged at right angles to the shaft proper. A pathologic fracture is evident. The proximal portion of the left radius was similarly involved.

Armstrong units, serum calcium, 15.0 mg, and phosphorus, 2.8 mg. The cephalin flocculation reaction was 4 plus in twenty-four hours. Calcium excretion in both urine and stool was increased. The urine showed the presence of Bence-Jones protein on several occasions. A blood count revealed 3,400,000 erythrocytes and 8,000 leukocytes, of which 24 per cent were polymorphonuclear, 4 per cent transitional and 70 per cent plasma cells with dense eccentric nuclei containing chromatin in spokelike fashion and bluish gray cytoplasm (fig. 1). Repeat blood counts were

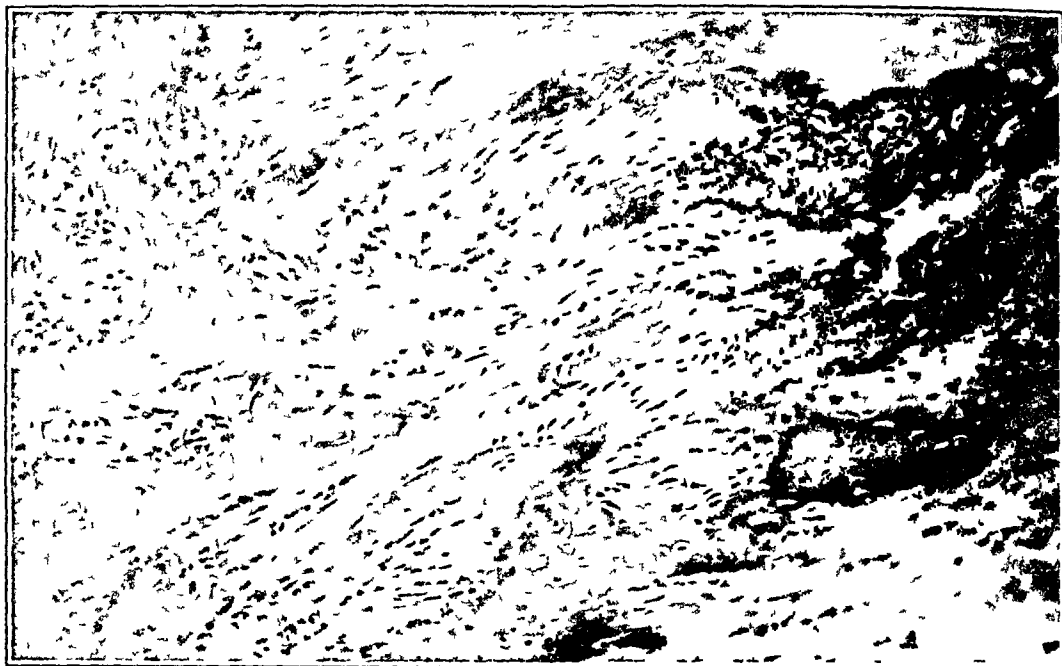


Fig 5—Osteoid and scar tissue with diffuse infiltration by myeloma cells in the vicinity of the fracture Hematoxylin and eosin stain, $\times 100$

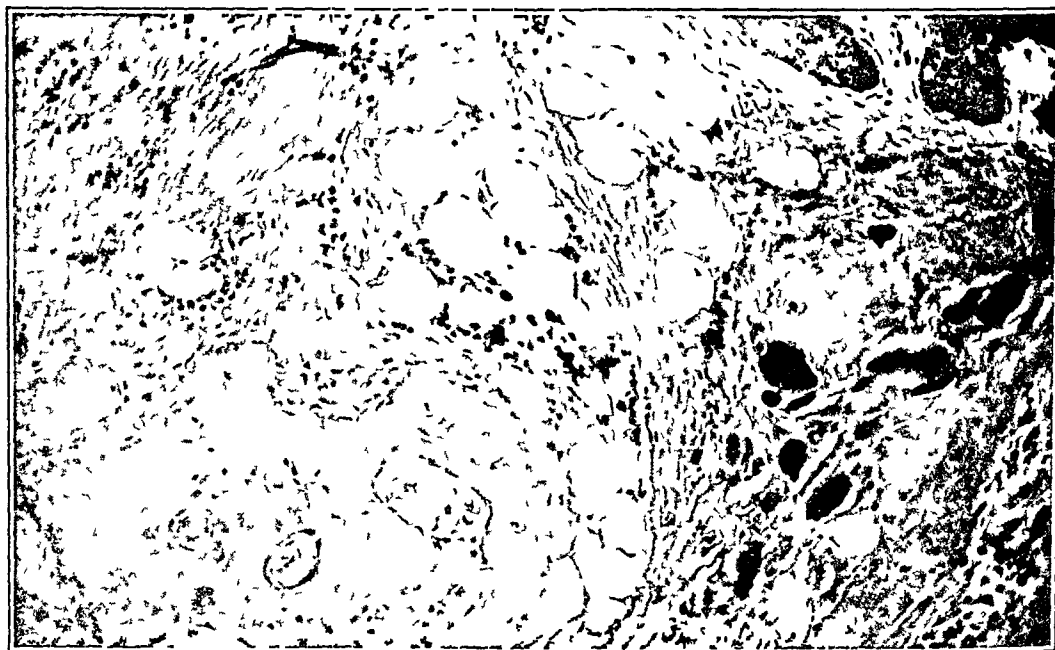


Fig 6—Section of periosseous tissues, showing newly formed trabeculae in the lower left and upper right corners, adipose tissue, fibrous tissue and voluntary muscle fibers There is diffuse infiltration by myeloma cells Hematoxylin and eosin stain, $\times 100$

done The total white cell count ranged from 9,000 to 35,000, and plasma cells comprised between 40 and 70 per cent of the total on various occasions Aspiration of sternal marrow revealed that the marrow was almost entirely replaced by plasma cells (fig 2)

One of the nodules on the patient's forehead was removed and on histologic study was found to consist of islets of plasma cells in a fibrous stroma

Roentgenographic examination of the pelvis showed no abnormalities Studies of the skull (fig 3) revealed a great number of small punched-out areas of less density than the surrounding bone There was an extensive area of destruction in the frontal bone The femurs, clavicles and right humerus disclosed numerous small cystic punched-out areas The left humerus (fig 4) showed a diffuse productive process involving the entire shaft and producing a shaggy appearance Dense bony spicules were arranged at right angles to the shaft proper along most of the bone There was a pathologic fracture at the lower end of the humerus The proximal portion of the left radius revealed a pathologic fracture and productive bone changes similar to those seen in the humerus

Biopsy of the left humerus was performed A series of sections prepared from random fragments removed from the vicinity of the fracture and several other points along the shaft disclosed unequivocal evidence of extensive new bone formation in association with myeloma (fig 5) Several areas of soft tissues were diffusely infiltrated by myeloma and here, too, there appeared to be a tendency toward laying down of osteoid and osseous tissue (fig 6) Review of many sections led to the impression that most of the new bone formation arose from the periosteum The marrow, wherever present, was extensively transformed into myeloma Several fragments presented an intermixture of areas of osteoid tissue, fibrosis and necrobiosis of the original cortex which suggested the usual tissue reactions to fracture The general impression was that a unique response on the part of the periosteum to irritation by infiltrating tumor resulted in the formation of the extraordinary deposits of bony tissue disclosed by the roentgenograms

Course—A week after admission the patient was found to have a painless pathologic fracture of the lower end of the left humerus She remained semistuporous throughout her stay in the hospital She was fed by clysis and infusion and was given several transfusions Stilbamidine® (4-4'-diamidinostilbene) therapy was started shortly before her death, which occurred three weeks after entry Autopsy was not done

COMMENT

We have read many protocols of autopsies in which multiple myeloma was seen without finding reference to new bone formation other than that occurring at the site of pathologic fracture and resulting in union of the fragments, a mechanism clearly unrelated to the disease process itself Harbitz⁵ and also Schmorl⁶ have described what they termed "thickening" occurring in the skull and in the tubular bones some distance from the area of bone absorption Close scrutiny of their material discloses no parallelism whatever to the case herein reported,

5 Harbitz, F Multiple primære svulster i ben systemet (myelosarkoma), Norsk Mag f Lægevidensk 1.89 and 169 (Jan-Feb) 1903

6 Schmorl Fall von Myelom, Munchen med Wchnschr 59:2891 (Dec 24) 1912

unequivocal evidence of new bone formation was not cited or adduced, there were no roentgenograms Geschickter and Copeland⁷ in 1928, in a review of all the cases of proved multiple myeloma appearing in the literature up to that time, stated, "The tumors themselves are bone destructive and frequently show up in the pictures as rounded, punched-out areas varying from the size of a pea to that of an orange. Sometimes they are more diffuse, giving a rarefied osteoporitic appearance to the roentgenogram, or, when multiple areas have become confluent, resembling mottling." In a recent report of 61 cases of multiple myeloma by Adams, Alling and Lawrence⁸ the roentgen findings are summarized as being those of, first, osteoporosis, second, small "flea-bitten" areas of rarefaction without evidence of new bone formation, third, and most characteristic, the "punched-out" area with its sharp margination without evidence of surrounding osteoblastic change, and, fourth, in a few cases, no roentgen changes of any type. Our case, therefore, appears to be unique in that new bone formation in multiple myeloma occurred in marked degree, as was conclusively shown by histologic and roentgenographic examination.

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Dr. Joseph C. Ehrlich gave valuable assistance in preparing the manuscript.

⁷ Geschickter, C. F., and Copeland, M. M. Multiple Myeloma, *Arch. Surg.* **16**: 807 (April) 1928.

⁸ Adams, W. S., Alling, E. L., and Lawrence, J. S. Multiple Myeloma: Its Clinical and Laboratory Diagnosis with Emphasis on Electrophoretic Abnormalities, *Am. J. Med.* **6**: 141 (Feb.) 1949.

PERIARTERITIS NODOSA

Study of Chronicity and Recovery, with Report of Two Cases

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DETROIT

THE PURPOSE of this communication is to reevaluate the prognosis in periarteritis nodosa in the light of the reports in the literature and the personal experiences noted herein. In the past, the course of the disease has been regarded as leading to a fatal termination. This, undoubtedly, is the outcome in the majority of instances. There have been cases, however, in which the disease has taken a chronic course, others with long, complete remissions and a few in which recovery has been reported. Two cases in which recovery occurred are presented.

In 1852, von Rokitsansky¹ first described the pathologic changes of the disease entity periarteritis nodosa. It remained for Kussmaul, however, to recognize it as a clinical syndrome. With Maier,² in 1866, he reported 2 cases of a "hitherto undescribed peculiar disease of the arteries which is accompanied by Bright's disease and is a rapidly progressive, general paralysis of the muscles." The disease as described was chronic, diffuse, obscure in origin and of serious prognosis.

There have been many excellent reviews of periarteritis nodosa, the best among them being those by Lamb,³ Ophuls,⁴ Gruber,⁵ Singer,⁶

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1 von Rokitsansky, C. Ueber einige der wichtigsten Krankheiten der Arterien, Denkschr d k Akad d Wissensch **4** 1, 1852

2 Kussmaul, A., and Maier, R. Ueber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, Deutsches Arch f klin Med **1**.484, 1866

3 Lamb, A. R. Periarteritis Nodosa. A Clinical and Pathological Review of the Disease, Arch Int Med **14** 481 (Oct) 1914

4 Ophuls, W. Periarteritis Acuta Nodosa, Arch Int Med **32** 870 (Dec) 1923

5 Gruber, G. B. Zur Frage der Periarteritis nodosa, mit besonderer Berücksichtigung der Gallenblasen- und Nieren-Betheiligung, Virchows Arch f path Anat **258** 441, 1925

6 Singer, H. A. Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations. Report of Two Cases, Arch Int Med **39** 865 (June) 1927

Strong,⁷ Curtis and Coffey,⁸ Middleton and McCarter,⁹ Spiegel,¹⁰ Harris, Lynch and O'Hare,¹¹ Grant¹² and Miller and Daley¹³

Klotz,¹⁴ early in 1917, stated that the mortality rate was 100 per cent. He recognized however, that that situation might prevail because a proper diagnosis was being reported only in the fatal cases at that time. Two reasons were advanced for this lack of clinical recognition. "As the typical lesions are found upon the vessels of internal organs, the skin being involved in only a few cases, no opportunity is given the clinician to analyze the lesions. Undoubtedly in many instances a similar localization and infection of milder character involves various systems of the arteries, but in the absence of marked clinical signs or serious pathological change, the cases proceed to recovery without our attention being called to the characteristic lesion." Thus it was early suggested that because of difficulty in diagnosis and because mild forms of the condition might go unrecognized, periarteritis nodosa might exist in other than an acutely fatal form.

Many writers have stressed the high fatality rate but have also mentioned cases in which there were chronic courses, remissions and apparent recoveries. Haining and Kimball¹⁵ stated the view that periarteritis nodosa is a progressive and incurable disease. That belief they supported with the data on rapidly fatal termination in most reported cases, in nearly all of which there was histologic evidence of acute inflammation as well as chronic reparative changes. However, they agreed that "in spite of the dubious prognosis, there can be no doubt that occasionally the process comes to a halt." Leishman,¹⁶ writing in 1937, stated "The disease seems almost invariably fatal although four undoubted cases have recovered and it seems likely that an occasional

7 Strong, G. F. Periarteritis Nodosa, *Canad. M. A. J.* **19**: 534 (Nov) 1928.

8 Curtis, A. C., and Coffey, R. M. Periarteritis Nodosa. A Brief Review of the Literature and a Report of One Case, *Ann. Int. Med.* **7**: 1345 (May) 1934.

9 Middleton, W. S., and McCarter, J. C. Diagnosis of Periarteritis Nodosa, *Am. J. M. Sc.* **190**: 308 (Sept.) 1935.

10 Spiegel, R. Clinical Aspects of Periarteritis Nodosa, *Arch. Int. Med.* **58**: 993 (Dec.) 1936.

11 Harris, A. W., Lynch, G. W., and O'Hare, J. P. Periarteritis Nodosa, *Arch. Int. Med.* **63**: 1163 (June) 1939.

12 Grant, R. T., Observations on Periarteritis Nodosa, *Clin. Sc.* **4**: 245 (Oct.) 1940.

13 Miller, H. G., and Daley, R. Clinical Aspects of Polyarteritis Nodosa, *Quart. J. Med.* **15**: 255 (Oct.) 1946.

14 Klotz, O. Periarteritis Nodosa, *J. M. Research* **37**: 1 (Sept.) 1917.

15 Haining, R. B., and Kimball, T. S. Periarteritis Nodosa, *Am. J. Path.* **10**: 349 (May) 1934.

16 Leishman, A. W. D. The Clinical Diagnosis of Polyarteritis Nodosa, *Lancet* **1**: 803 (April 3) 1937.

case may recover unrecognized" Sandler,¹⁷ too, stressed the high fatality rate, stating that when the disease is confined to structures less vital than the heart and kidneys a complete cure is possible once the lesions have healed. Although the patient may survive the acute stage, he wrote, when the vital organs are involved he will eventually die of cardiac or renal failure due to the healed lesions of the arteritis. Similarly, Lummis¹⁸ mentioned the almost invariably fatal outcome. He stated the belief that the favorable outcomes were due to remissions. "It is not unlikely that there exists a form milder than the usual fatal one but it is at present below the diagnostic level." Baker,¹⁹ in a review in 1942, noted that the disease was fatal in the majority of cases. However, he estimated that 10 per cent of patients recovered.

Periarteritis nodosa is not invariably fatal. In the past, interest in the disease was primarily on the part of the pathologist, so that only the cases coming to necropsy were reported. However, by 1940, Grant¹² could state that of 350 reported cases the diagnosis was established ante mortem in 50. Many more cases can be added to this list as of the time of writing. Further clinical recognition will result from an elevated "index of suspicion" and the more frequent use of biopsy. Weiss²⁰ wrote that the prognosis of the disease would improve when it was recognized oftener clinically. Remissions, long intermissions and exacerbations he recognized as being common in the natural history of periarteritis nodosa.

Two cases are presented as additional instances of recovery from periarteritis nodosa.

REPORT OF CASES

CASE 1—J. McC., a white man of 21, has been asymptomatic for the past year at the time of this report, having recovered from two episodes of periarteritis nodosa at the ages of 7 and 20, he remained entirely well for the interval of twelve years.

First Admission (table 1)—The patient was admitted to the Boston City Hospital for the first time in January 1935 at the age of 7. A history of a normal birth was obtained, measles and whooping cough were the only previous illnesses.

The family history was significant only in that the mother had hay fever and asthma, being sensitive to the pollen of ragweed and goldenrod.

One week prior to admission, the child complained of a sore throat. This was followed by soreness and stiffness of the legs, feverishness, restlessness and

17 Sandler, B. P. Periarteritis Nodosa. Report of Case Diagnosed Clinically and Confirmed by Necropsy, *Am J M Sc* **195**:651 (May) 1938.

18 Lummis, F. R. Periarteritis Nodosa, *Ann Int Med* **10**:105 (July) 1936.

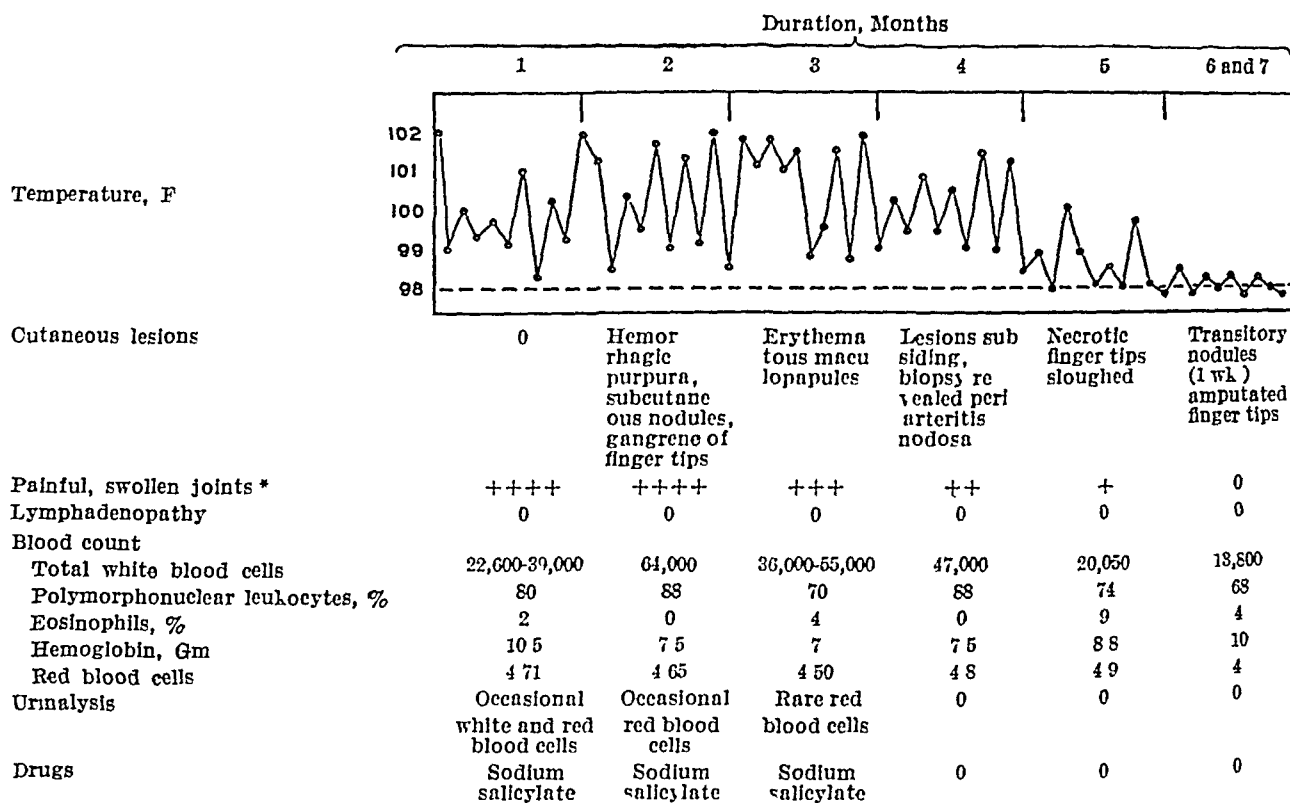
19 Baker, L. A. Periarteritis Nodosa, with Report of Two Cases, *Ann Int Med* **17**:223 (Aug) 1942.

20 Weiss, S. Arteritis. Diseases Associated with Inflammatory Lesions of the Peripheral Arteries, *New England J Med* **225**:579 (Oct 9) 1941.

anorexia The child was confined to bed with increasing pain in the right knee, the left knee then became painful and tender On the day of hospitalization, abdominal pain appeared

Physical Examination The child was well developed but poorly nourished and acutely ill The left wrist, the right ankle and both knees were swollen, warm, tender and painful on motion The tonsils were hypertrophic and hyperemic The heart was normal in size At the apex was a soft systolic murmur,

TABLE 1—*Course of the Disease in Case 1 at the Time of the First Hospitalization, When the Patient Was 7*



* Basis of 0 to ++++

transmitted upward to the base The blood pressure was 100 systolic and 64 diastolic

Laboratory Studies The hemoglobin concentration was 10.6 Gm per cubic centimeter of blood (71 per cent), there were 4,700,000 erythrocytes and 22,600 leukocytes per cubic millimeter, the differential smear contained 80 per cent neutrophils, 14 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils

Course During the first month of hospitalization, the condition of the joints remained unchanged Sodium salicylate was administered orally, and methyl salicylate was applied locally Tachycardia with a rate of 110 to 120 persisted The total white cell count rose steadily to 39,200 No albuminuria or glycosuria was noted Blood cultures were sterile

In the second month, lesions of hemorrhagic purpura appeared on the extremities and back. The finger tips became painful and discolored, and dry gangrene followed. Subcutaneous nodules appeared scattered over the body with some located in relation to the blood vessels.

During the third month, the symptoms in the joints began to subside, and the hemorrhagic purpura subcutaneous nodules began to resolve. Erythematous maculopapular lesions appeared on the chest. The gangrenous finger tips continued to separate. Tachycardia with a rate of 100 to 120 persisted. On roentgenograms the chest and joints appeared normal. The electrocardiogram revealed sinoatrial tachycardia, a P-R interval of 0.12 second and right axis deviation.

The fourth month of hospitalization was characterized by the persistence of the fever and tachycardia. Biopsy of a subcutaneous nodule from the abdomen was done (fig 1). Pain was present in both hands, and the necrotic terminal phalanges continued to separate.

During the fifth month, the pulse rate varied from 80 to 120. The necrotic finger tips sloughed, and healing supervened. The joints were only slightly tender. The differential smear contained 74 per cent neutrophils, 13 per cent lymphocytes, 9 per cent eosinophils and 4 per cent monocytes. The electrocardiogram revealed sinoatrial tachycardia with a P-R interval of 0.12 second.

During the last two months of hospitalization (the sixth and seventh), the pulse was normal. At the end of the sixth month, a new crop of skin lesions appeared. These were subcutaneous nodules measuring 1 to 2 cm in diameter and covered by erythematous skin. The amputated phalanges healed.

The patient's general condition improved. He remained ambulatory and active about the ward. His appetite was good, and a marked gain in weight occurred. The leukocyte count fell to 13,800. The differential smear contained 68 per cent neutrophils, 26 per cent lymphocytes, 4 per cent eosinophils and 2 per cent monocytes. The examination of the urine was entirely noncontributory.

Interval—The patient was discharged in the care of his mother. He enjoyed good health in the following twelve years, and his physical development was normal. In recent years, he worked at chrome plating, which necessitated the use of nitric, sulfuric and chromic acids, as a result, burns of the hands were not uncommon.

Second Admission (table 2)—Pain and weakness of both forearms appeared in April 1947. The patient's family physician made a tentative diagnosis of rheumatic fever and instituted penicillin therapy. With the increasing severity of symptoms and the onset of severe toothache, the patient was admitted to the hospital two weeks later.

The symptomatic tooth was extracted. The report was "pulpitis, right third molar, without dental cause." The tooth did not show carious lesions clinically or roentgenographically, the changes being consistent with ischemia.

Physical Examination On admission to the medical ward, the patient appeared acutely ill and in considerable pain. The lower extremities were abducted at the hips and flexed at the knees. The upper extremities were flexed on the chest. Slight movement was resisted because of pain. The oral temperature was 101 F, the pulse rate 100 and the respiration rate 25. The blood pressure was 160 systolic and 85 diastolic. The skin was warm and dry. On both calves were circumscribed, indurated, nontender nodules, which were 1 cm in diameter and pink. Reddish violet maculopapular lesions, 1 to 2 cm in diameter and discrete and nontender, some of which showed typical iris configuration, were present on the medial aspect of the right foot. On the volar surface of each forearm was an erythematous

blush Pronounced generalized tenderness of the muscles was present, especially prominent in the paravertebral muscles of the back, the sternocleidomastoid muscles and those of the anterior abdominal wall and the extremities There was swelling of the muscle groups of the extremities and increased firmness, to a rubbery consistency Cervical resistance to flexion was noted Many teeth were carious Moderate enlargement and tenderness of the cervical, axillary and inguinal lymph nodes were present The lungs were clear, and there were no cardiac

TABLE 2—*Course of the Disease in Case 1 at the Time of the Second Hospitalization, When the Patient Was 20*

	Duration, Months			
	1	2	3	4
Temperature, F				
Cutaneous lesions	Nodules, maculo papules, erythema, biopsy revealed acute periarteritis nodosa	Increased numbers of nodules and macules appeared and faded, gangrene formed and sloughed	Lesions subsiding, biopsy revealed healing periarteritis nodosa	0
Painful, swollen muscles and joints *	++++	+++ to ++	+ to 0	0
Lymphadenopathy *	++	++	0	0
Blood count				
Total white blood cells	26,300	12,000-16,000	7,450	8,750
Polymorphonuclear leukocytes, %	89	68	68	67
Eosinophils, %	0	3	6	6
Hemoglobin, Gm	14	9	12.5	12.5
Red blood cells	4.6	4	4.5	4.5
Urinalysis	0	0	0	0
Drugs	Penicillin, sodium salicylate 1st & 2nd wk, tripeleannamine hydrochloride 3rd & 4th wk, meperidine hydrochloride ("demerol hydrochloride")	Tripeleannamine hydrochloride, meperidine hydrochloride, codeine	0	0

* Basis of 0 to +++++

murmurs The ophthalmoscopic examination was noncontributory The pulse was easily palpable in the radial, the posterior tibial and the dorsalis pedis arteries

Laboratory Examination The leukocyte count was 26,300 The differential smear contained 14 per cent juvenile and 75 per cent mature neutrophils and 11 per cent lymphocytes The corrected sedimentation rate (Wintrobe method) was 30 mm per hour, the hemoglobin concentration 14 Gm (95 per cent), the hematocrit reading 40 and the icterus index 5 Other blood chemistry values were nonprotein nitrogen 34 mg, total protein 5.6 Gm (albumin 2 Gm, globulin 3.6 Gm) and cholesterol 219 mg per hundred cubic centimeters The blood cultures

were sterile. Cultures of material from the throat were positive for alpha hemolytic streptococci, diphtheroids and *Neisseria catarrhalis*. Biopsy of a subcutaneous nodule was done (fig 2).

Course The course for the next month was stormy. The temperature remained elevated, reaching peaks of 102 to 103 F (oral). The pulse rate showed a proportional rise. The weakness was progressive, the patient had to be turned in bed. Irritability, generalized pain and tenderness made nursing care difficult. Anorexia was pronounced and the loss of weight was progressive.

At the conclusion of the first week of hospitalization, there occurred three consecutive seizures. These were characterized by a loss of consciousness and by generalized convulsive movements of three to five minutes' duration, the interval between seizures was approximately five minutes, and stupor followed them. The tendon reflexes were noted to be hypoactive on the right side, and bilateral extensor plantar reflexes were obtained. Examination of the spinal fluid revealed an initial pressure of 195 mm of water, 3 lymphocytes per cubic millimeter and a total protein value of 15 mg per hundred cubic centimeters. The responses to the Pandy and colloidal gold tests were negative. On the following day, there was evidence of muscular weakness in the lower right side of the face. The tendon reflexes were equal on the two sides, and the plantar responses were flexor. The sensory modalities were normal.

The cutaneous lesions on the medial aspect of the right foot and the flexor surface of both forearms became ecchymotic. The lesions on the right foot became confluent, with a well defined border. On the calves and the flexor surfaces of the arms, pea-sized nodules appeared, which were pink and only slightly tender, these did not appear to follow any anatomic structure. Toward the end of the first month, violaceous macules were noted on the pectoral girdle. The pigmented lesions on the volar surface of the left forearm began to fade, whereas those on the right turned brown and began to slough.

The generalized tenderness of the muscles diminished slowly. Induration and swelling remained in the forearms and the muscles of the calves. In these muscle groups, the tenderness was most marked. Flexion contractures developed in the fingers, wrists, elbows and knee joints. Passive movement produced pain.

The initial medication was as indicated in table 2. Administration of the antihistamine agent tripeleminamine hydrochloride (pyribenzamine hydrochloride®) was begun, a daily dose of 350 mg being given.

During the second month of hospitalization, there was improvement in the patient's strength and appetite. Less pain was experienced, but liberal amounts of acetylsalicylic acid and codeine were still necessary. The necrotic epidermis on the volar surface of the right forearm sloughed, leaving a pink, granulating area. On the medial aspect of the right foot, the cutaneous lesions continued to fade and the epidermis desquamated. Toward the end of the second month, a new crop of nodules similar to those previously described appeared on the arms and calves. There was no associated systemic exacerbation.

With the application of splints and with physical therapy, the flexion deformities improved and some degree of motion returned at the joints.

The urine was consistently normal. The hematocrit reading was 31 and the erythrocyte count 4,000,000. The differential count showed 6 per cent juvenile and 60 per cent mature neutrophils, 28 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 25 mm per hour. The total protein value was 7.45 Gm (albumin 3.64 Gm, globulin 3.81 Gm). The blood cultures remained sterile.

At the end of the second month of hospitalization, analgesics were still necessary for the control of pain

In the third month, rapid improvement took place. With a better appetite, the patient showed a gain in weight. The pain disappeared entirely. The pulse returned to normal. All rigidity of the muscles disappeared. A full range of motion returned to all joints, and the patient became ambulatory. The hematocrit reading rose to 33. The differential count showed 66 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils. The value for nonprotein nitrogen was 29 mg per hundred cubic centimeters. The sulfobromophthalein test for liver function (5 mg was given per kilogram of body weight) showed 4 per cent dye retention in forty-five minutes. The phenolsulfonphthalein test (intravenous injection) revealed that 40 per cent of the dye was excreted in fifteen minutes and 85 per cent in two hours. A biopsy of a resolving subcutaneous nodule was made (fig 3).

The fourth and final month of hospitalization was one of convalescence. The patient was fully ambulatory and aided in the ward work. A full range of motion returned to all the extremities. The appetite was good, and a gain in weight was recorded. The hands remained mottled and were constantly cool and moist. The heart and lungs were not remarkable. Results of the neurologic examination were noncontributory, the facial weakness having disappeared.

During the entire illness, there was no evidence of pulmonary, cardiac or renal involvement. Roentgenograms of the chest showed the lung fields to be clear and the cardiac size and configuration to be normal. Repeated electrocardiographic tracings were normal (the P-R interval was 0.13 to 0.16 second, the Q-S interval 0.09 second and the T waves upright in all leads, there was right axis deviation). The blood pressure, which originally showed a slight systolic elevation (160 systolic and 85 diastolic), was normal on the discharge of the patient (130 systolic and 80 diastolic).

Condition After Discharge—One year after discharge from the hospital, the patient was entirely well and at work driving a delivery truck. On exposure to cold, he stated, his hands became a mottled blue color and were uncomfortable. This disappeared readily on warming. Physical and laboratory examinations were entirely noncontributory. The pulse rate was 80 and the blood pressure 124 systolic and 74 diastolic. The urine was normal. Examination of the blood revealed 14 Gm of hemoglobin (95 per cent) with a hematocrit reading of 42. The leukocyte count was 7,100 and the differential count normal.

Microscopic Examination—The first biopsy (fig 1), done in April 1935, showed a small artery, the lumen of which was of pinpoint size owing to endothelial proliferation. There was infiltration of all coats and of the surrounding fat by lymphocytes, neutrophils and eosinophils. Fibroblastic proliferation was present in the adventitia and muscularis. Other sections showed the acute inflammatory reaction involving medium-sized subcutaneous arteries. One such vessel had the lumen occluded by a partially organized thrombus and large numbers of neutrophils. A heavy infiltration of neutrophils involved all coats, from the intima to the adventitia.

The second biopsy (fig 2) made twelve years later during the acute phase of the second admission, showed an acute, necrotizing, inflammatory process involving a small artery of skeletal muscle. Fibrinoid necrosis of the media and subintima was pronounced, with infiltration of neutrophils in all the coats and the surrounding tissue.



Fig 1—Photomicrograph of subcutaneous nodule made during the fourth month of the first admission in case 1, showing a small artery with endothelial proliferation and cellular infiltration $\times 200$



Fig 2—Photomicrograph of section of muscle made during the acute stage of the second admission in case 1, showing acute necrotizing periarteritis $\times 200$

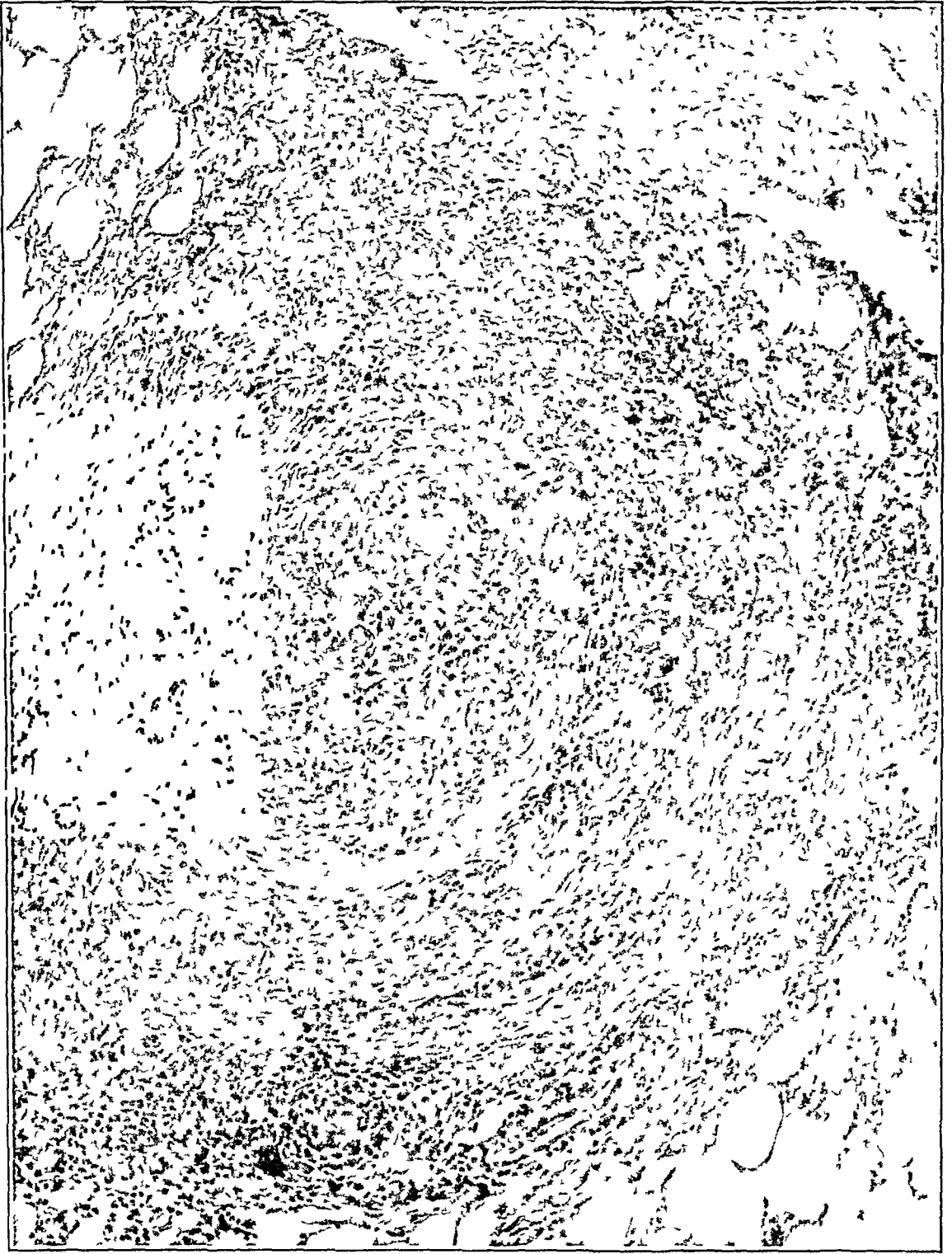


Fig 3—Photomicrograph of section of skin obtained during the healing stage of the second admission in case 1, showing a small artery with a thrombosed lumen, subacute inflammatory infiltration and fibrosis $\times 200$

The third biopsy (fig 3), made during the healing phase of the second admission, showed a small subcutaneous artery with the lumen occluded by cellular fibrous tissue. Several small, irregular, endothelium-lined spaces, some containing erythrocytes were present within the thrombus. The intima and portions of the muscularis were replaced by cellular fibrous tissue. A similar type of fibrosis was evident in the surrounding fat. Throughout the artery were a few lymphocytes, neutrophils and eosinophils. A small arteriole in the adventitia showed similar fibrosis and infiltration in the wall. Several small subcutaneous vessels showed perivascular collections of lymphocytes. Stains for elastic tissue demonstrated the fraying and breaking up of the elastica interna. The elastic tissue was decreased in amount.

A final biopsy specimen, taken after the subsidence of the disease through an area of skin and muscle known to have been previously involved, showed no significant pathologic features.

CASE 2—M. D., a white girl of 15, experienced lower abdominal pain on the right side followed by nausea, vomiting and a sensation of chilliness. The illness was of one week's duration when the patient was admitted to the hospital.

The physical examination showed tenderness in the right lower quadrant of the abdomen. The blood pressure was 110 systolic and 70 diastolic. The leukocyte count was 8,000.

An appendectomy was performed, and convalescence was uneventful. Eleven years after discharge (at the time of this report), the patient had remained well.

Microscopic Examination—Sections of the appendix showed small arteries with fibrinoid necrosis of the wall. Associated was periarterial infiltration with plasma cells, lymphocytes and neutrophils. Some vessels showed infiltration of the wall with a similar type of exudate. An occasional artery was occluded by granulation tissue in which a few neutrophils, plasmocytes and lymphocytes could be seen.

REVIEW OF CASES IN THE LITERATURE

A number of cases of periarteritis nodosa reported in the literature are of special interest because of the course of the disease. Chronicity with periods of remission of many years' duration and instances of recovery have been reported. Cases in which recovery occurs are often difficult to evaluate, in a disease that shows remissions and exacerbations so frequently, the permanence of recovery must be questioned unless a long follow-up study is made. In the unusual case reported in this paper (case 1), the disease reappeared after a period of twelve years.

The average duration of life following the onset of symptoms is under one year. Gruber,²¹ in 1926, reported the average duration in 57 cases to be 47 months. Curtis and Coffey,⁸ reporting on 17 cases, obtained an average of sixteen months, Strong,⁷ reporting on 21 cases, computed an average of five months, and Harris, Lynch and O'Hare,¹¹ summarizing 101 cases found the average duration to be 86 months.

21 Gruber, G. B. *Kasuistik und Kritik der Periarteritis Nodosa*, Zentralbl f. Herz- u. Gefasskr. **18** 145, 1926.

Representative case reports have been abstracted from the literature to illustrate chronicity as well as recovery. Table 3 contains reports of cases with chronic courses, i. e., illnesses of many years' duration with persistent symptoms or periods of remission and exacerbation.

Since periods of remission are common in the course of the disease, cases in which recovery occurred are arbitrarily separated into two groups depending on whether an observation period of at least one year was reported. Table 4 lists the cases in which recovery was reported with short follow-up periods. Cases of periarteritis nodosa in which the patients were reported as recovered with a follow-up period of one year or more are briefly summarized.

TABLE 3—*Reported Cases of Periarteritis Nodosa with Chronic Courses*

Author	Patient		Course
	Sex	Age, Years	
Schmorl (Verhandl d deutsch path Gesellsch 6 :203, 1903)	F	53	Patient died after 2 years, acute portal thrombosis, only healed lesions of arteritis found at autopsy
Arkin (Am J Path 6 401 [July] 1930)	M		Patient died after 4 years, myocardial and renal insufficiency, histologic studies showed healed end stages of periarteritis nodosa
Macaigne and Nicaud (Presse méd 40 665 [April 27] 1932)	F	27	Initial attack followed by latent period of 5 years with crises for next 10 years
Grant ¹²	F	17	Periodic attacks for 8 years with active disease at end of period
Miller and Daley ¹³	M	14	Chronic course of 8 years' duration with disease reported active at end of period
	M	40	Recurrent attacks for 5½ years with active disease at end of period
Galán (Bol Soc cubana de pediat 17 :293 [Aug] 1945)	M	9	Recurrent episodes over 4 years with evidence of activity at end of period
King (J Mt Sinai Hosp 15 :97 [July-Aug] 1948)	F	51	Duration of 2 to 3 years with evidence of activity at end of period

Erlandsson ²²—This white patient died one year after the diagnosis of periarteritis nodosa had been established by biopsy. At necropsy, no lesions of the disease were observed. Death was due to metastases from carcinoma of the uterus.

Lindberg ²³—A white boy of 15 had been sick for a period of four years. Biopsy of subcutaneous nodules established the diagnosis. At the time of publication of the report, the patient had been entirely well for one year.

Harris, Lynch and O'Hare ¹¹—A student of 19, of Greek extraction, had a past history of painful joints and loss of weight of five months' duration. An examina-

²² Erlandsson, S. Neurologische Krankheitsbilder bei Periarteritis nodosa, *Acta psychiat et neurol* **6** 369, 1931.

²³ Lindberg, K. Ueber eine subkutane Form der Periarteritis nodosa mit langwierigem Verlauf, *Arch d path Inst d Univ Helsingfors* **7** 159 1933.

tion had revealed diffuse tenderness of the muscles, hepatomegaly, splenomegaly, fever, tachycardia and a leukocyte count of 18,400. Transitory subcutaneous nodules had appeared. After three months, there was considerable improvement in the patient's condition. Seven months later, similar symptoms of generalized weakness and pain and tenderness of the muscles reappeared. Numerous erythematous circinate lesions appeared on the trunk and extremities. Biopsy established the diagnosis. The patient improved and when seen four years after the onset of the symptoms he was perfectly well.

*Grant*¹²—A white engineer of 61 had a previous history of asthma of seven years' duration. Pain and pallor in the fingers of the left hand had developed on

TABLE 4—*Reported Cases of Periarteritis Nodosa in Which Patients Recovered but Subsequent Observation Lasted Less Than One Year*

Author	Patient		Course
	Sex	Age, years	
von Haun (Virchows Arch f path Anat 227 90, 1919)	M	30	Patient ill 3 months, returned to duty as soldier
Carling and Hicks (Lancet 1.1001 [May 19] 1923)	M	30	Patient returned to work asymptomatic 9 months after onset
Schottstaedt (California & West Med 36 186 [May] 1932)	M	41	Two episodes separated by period of 2 months, 1 month after second attack, patient asymptomatic and returned to work
Motley (J A M A 106 898 [March 14] 1936)	M	31	Single severe protracted course, patient returned to work 10 months after discharge
Vining (Arch Dis Childhood 13 31 [March] 1938)	F	7	Recurrent attacks over 2 years, patient entirely asymptomatic at end of period
Grant ¹²	M	38	Illness of 5 months' duration, except for residual palsies, patient well 5 months later
	M	46	Patient returned to work 1 month after onset of illness, remained in good health 8 months later
Miller and Daley ¹³	M	23	Patient severely ill for 3 months, 7 months later reported entirely well
White (Minnesota Med 30 303 [March] 1947)	F	73	Patient hospitalized three times in 16 months, entirely asymptomatic 6 months after discharge

exposure to cold. A single subcutaneous nodule had appeared on the dorsum of the left forearm and gradually subsided. Two years later, there appeared pain, weakness and sensory changes in the left arm and abdominal distention and tenderness. The asthma increased in severity. Subcutaneous nodules appeared on the left upper extremity, and biopsy of one of them established the diagnosis. Improvement followed, and three years after the onset of the first symptom the patient was at work. He remained well.

*Goldman, Dickens and Schenken*²⁴—A Negro of 22 gave an initial complaint of weakness and dull, aching muscular pain and tenderness. There followed chills, fever, abdominal pain, loss of weight and the appearance of subcutaneous nodules

²⁴ Goldman, B. A., Dickens, K. L., and Schenken, J. R. The Apparent Cure of Periarteritis Nodosa with Sulfapyridine, *Am J M Sc* 204 443 (Sept.) 1942.

Biopsy of a nodule established the diagnosis. A total of 156 Gm of sulfapyridine was given in thirty-two days, improvement followed. Nineteen months after discharge, the patient was in excellent health, performing manual labor.

MacKeith ²⁵—A white engineer of 27 had a history of chronic cough. A sudden onset occurred, including pain in the right groin, right hemiparesis, localized edema of the right arm and the appearance of two subcutaneous nodules on the right calf. Leukocytosis was present (the count was 12,000, with a normal differential count). Pyrexia and tachycardia were present. Histologic examination of a subcutaneous nodule established the diagnosis. Five weeks after admission, the patient left the hospital quite well. Two and one-half years later he was reportedly asymptomatic.

A white engineer of 58 gave a history of recurrent bronchitis of two years' duration. The sudden onset of paresis of the hands, legs and feet was associated with sensory changes. Pitting edema of the upper extremities and the ankles was present. The value for blood urea nitrogen was elevated to 70 mg per hundred cubic centimeters, and albuminuria was present. Diarrhea appeared and the muscular weakness increased in severity, wasting was severe. By the second month, improvement was noted. Six months later, the patient was ambulatory but both hands were wasted and contracted. One year later, the patient could write, shave and walk a mile.

Contratto ²⁶—A Chinese of 40, with a past history of pulmonary tuberculosis experienced fever, malaise and swelling of the right side of the neck, nodules appeared on the right forearm. Biopsy of a nodule established the diagnosis of periarteritis nodosa. Improvement followed, and the patient returned to work at the end of three months. After nine months of good health, he became ill once more for four months. An interval of two years of good health was followed by fever, enlargement of the posterior cervical lymph nodes, pains in the legs, loss of weight and appearance of subcutaneous nodules. Biopsy of a subcutaneous nodule again demonstrated active periarteritis nodosa, whereas a cervical lymph node showed active tuberculosis. At the end of four months, the patient felt well. Two years later, on examination, he was found to be entirely normal.

Goodman ²⁷—A white student of 17 was given sulfadiazine for a sore throat. Six weeks later, the soreness appeared again. The patient became seriously ill after two days of sulfadiazine therapy, and use of the drug was discontinued. An erythematous skin rash appeared and progressed, to become purpuric. Fever, muscular pain and migratory swelling and pain in the joints appeared. The blood pressure rose to 164 systolic and 104 diastolic. Hematuria and loss of weight were noted. The white cell count ranged from 10,300 to 19,900 and the platelet count from 76,000 to 147,000. Biopsy of the left deltoid muscle established the diagnosis. Inadvertently, sulfadiazine was administered again, in spite of the development of

25 MacKeith, R. Localized Subcutaneous Oedema with Weakness of Limb Muscles. Syndrome Due to Polyarteritis Nodosa, *Brit M J* **1** 139 (Jan 29) 1944.

26 Contratto, A. W. Periarteritis Nodosa. A Report of Two Cases, One with Special Reference to Sensitivity Factors, *Arch Int Med* **80** 567 (Nov) 1947.

27 Goodman, M. J. Periarteritis Nodosa with Recovery. Report of an Unusual Case Apparently Due to Sensitivity to Sulfadiazine, *Ann Int Med* **28**:181 (Jan) 1948.

an urticarial rash, it was continued. One week later, improvement was noted and the temperature became normal. Twenty-eight months later, the patient was in good health.

ETIOLOGY

Most evidence at the time of writing supports the experimental view that periarteritis nodosa represents a nonspecific hypersensitivity reaction to many agents. Gruber⁵ suggested early that periarteritis nodosa might result from a hyperergic reaction of the arteries to the various infectious or damaging agents. The role of bacterial antigens has been stressed. Of the instances reported, many were preceded by a respiratory infection, erysipelas, scarlet fever, tuberculosis or syphilis. The disease has followed the administration of antipneumococcus serum. The lesions have been produced experimentally by the administration of the sulfonamide drugs, organic arsenicals, desoxycorticosterone iodine thiourea and other substances.

PATHOLOGY

The disease produces cellular infiltration, necrosis, aneurysms and thrombosis of blood vessels. It involves segments of arterioles, small, medium and large arteries and, very rarely, veins. Usually many organs, systems or tissues are affected simultaneously. Evidences of acute, subacute and fibrosing stages may be present at any one time.

Microscopic study of the lesions initially shows an acute injury of varying severity involving the vessel wall. When necrosis or severe damage to the vessel wall exists, reparative fibrosis may follow. Thrombosis is common and the formation of aneurysms the exception. The degree of necrosis and thrombosis determines the functional state of the involved vessel, both during the acute phase and subsequently. In those lesions in which thrombosis and necrosis are absent, there may be complete healing. Usually the thrombosed or severely injured artery does not regain its full function.

The pathologic process appears to begin as edema of the vessel wall. This is followed by a fibrinoid degeneration of the media, destruction of the elastic laminae and infiltration of the perivascular region with inflammatory cells. The necrotic tissue is replaced by granulation tissue, and the acute inflammatory exudate, by a subacute and chronic exudate of histiocytes, lymphocytes and plasma cells. If thrombosis has occurred, organization with recanalization may follow. The weakened vessel wall may give way, with the formation of aneurysms or with hemorrhage. In the healed stage, there is frequently thickening of the arterial wall due to intimal proliferation and subintimal medial and periadventitial fibrosis.

Localized periarteritis nodosa, or disease confined to a single organ presents the same histologic picture as the generalized form. At the time of this report, there is little evidence in favor of classification of the generalized and localized types as different pathologic states.

RECOVERY

Periarteritis nodosa need not result in death. The natural history of the disease evolves from an initial degenerative and inflammatory phase to those of granulation and healed granulation. The histologic changes, therefore, show a progression toward healing.

The duration of the illness and its ultimate outcome are closely correlated with the degree of involvement of vital organs and the resultant impairment of function of these organs. Mild cases of periarteritis nodosa with minimal pathologic changes undoubtedly exist. Clinically, the manifestations are difficult to recognize when mild, the disease may thus go undiagnosed. As an exacerbation in a known case minimal changes have been noted.

Healing may occur clinically as well as histologically when the disease is confined primarily to nonvital organs or tissues. When extensive involvement of the renal, pulmonary, cardiac or intra-abdominal arteries occurs, the mortality is great. In those instances, however, in which the peripheral arteries supplying nonvital structures are mainly involved, recovery may be expected.

On both admissions, involvement predominantly of the peripheral arteries was noted in case 1. The course was febrile, with pronounced leukocytosis, polymyositis and cutaneous manifestations. Complete recovery followed each episode. A period of twelve years of good health intervened between admissions.

Recovery in cases with extensive involvement of vital structures occasionally occurs. However, death may follow as a result of the histologic healing causing vascular insufficiency of such organs as the heart, kidneys or liver.

Periarteritis may involve any organ, cases have been reported in which the process was local and not general. Spiegel¹⁰ reported 2 cases in young people in which the appendix alone was involved. In both, recovery was uneventful. Powell and Pritchard²⁸ reported a case in which the disease involved one kidney. Nephrectomy was performed because of hematuria. Ten months after the onset of symptoms, the patient was well and had returned to work.

28 Powell, R. E., and Pritchard, J. L. Periarteritis Nodosa, with Report of Case Involving One Kidney, *Brit J Urol* 4: 317 (Dec.) 1932.

M D, the patient in case 2, recovered from an appendectomy and remained well eleven years later. Microscopic examination of sections of the appendix showed lesions indistinguishable from those seen in the more generalized form of periarteritis nodosa.

THERAPY

During the acute phase, treatment must be mainly supportive. Since pain is frequently severe, sedation and the liberal use of analgesics are indicated. The maintenance of proper nutrition is important. The disease is a wasting one, and its course may be protracted. Flexion deformities occur, and unless proper orthopedic appliances are used and correct physical therapy is instituted, loss of function may result.

Although the causation is still unknown, there is good reason to suspect a hypersensitivity reaction. Early recognition and removal of the antigenic agent would be indicated. A history of drug sensitivity or the use of some medication prior to the onset of the disease should be regarded with suspicion. The antibiotic drugs may be of value when the antigenic agent is bacterial.

After recovery, hygienic measures for the prevention of infection should be instituted. The early recognition and vigorous therapy of an established infection are important. The removal of foci of infection in the case of a patient protected by the prophylactic administration of penicillin would appear to be indicated.

Any cures in periarteritis nodosa ascribed to various drugs must be viewed with suspicion, since the natural course of the disease may be one of remissions and exacerbations. During the early phase of the second admission in case 1, an antihistaminic agent was used. No conclusions are justifiable as to its value at this time.

SUMMARY AND CONCLUSIONS

Two unusual cases in which recovery took place are reported. The patient in case 1 had two histologically proved episodes of periarteritis nodosa separated by an interval of twelve years. One year after discharge from the second hospitalization, the patient was entirely asymptomatic. The patient in case 2, who had localized periarteritis of the appendix, was well eleven years after discharge.

The literature is reviewed to illustrate chronicity as well as recovery in periarteritis nodosa. The etiology and pathology are discussed, and suggestions for therapy are presented.

Periarteritis nodosa is not invariably an acutely fatal disease. The course may be chronic with periods of remission and exacerbation. Recovery may occur.

Recovery may be expected under the following circumstances: confinement of the disease predominantly to nonvital structures, minimal involvement of organs followed by healing, and localization of the disease to part of a single organ.

Recovery can occur despite the involvement of vital structures, but death may follow in the inactive phase many years later from vascular insufficiency to such organs as the heart, kidneys or liver.

NOTE.—At the time of publication it is well over two years since J. McC (case 1) was discharged from hospital. He remains in good health.

Dr. Dante Campagna-Pinto, Assistant in Pathology at the Mallory Institute of Pathology, Boston City Hospital, supplied the descriptions of the microscopic sections.

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CORONARY HEART DISEASE AND XANTHOMA TUBEROSUM ASSOCIATED WITH HEREDITARY HYPERLIPEMIA

Study of Thirty Affected Persons in a Family

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CLINICAL investigations concerning disturbances in lipid metabolism have opened a new chapter in the etiology of coronary heart disease. Recent studies have revealed an extremely high incidence of xanthomas and specific types of heart disease associated with hyperlipemia, especially hypercholesteremia.

The earlier investigators were concerned mainly with the etiology of xanthomatous lesions of the skin and tendons. These deposits have long been considered medical curiosities, and even today little is known concerning their formation. Tuberous xanthomas were first described by Addison and Gull,¹ in 1851, but it was not until 1920 that Chauffard, Laroche and Grigaut² and Burns³ demonstrated that there was an increased amount of total serum cholesterol in patients with xanthomas. In 1929, Wile, Eckstein and Curtis⁴ stated that the formation of xanthomas could not be explained solely by the theory of hypercholesteremia and that a defect in fat metabolism, in which cholesterol undoubtedly played a part, was apparently responsible.

In general, patients having xanthomas of tendons and tendon sheaths have an elevated number of blood lipids, especially serum cholesterol. Occasionally one sees these lesions in the absence of hypercholesteremia,

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1 Addison, T., and Gull, W. On a Certain Affection of the Skin. Vitiligoidea— α , Plana, β , Tuberosa, Guy's Hosp. Rep. **7** 265-276, 1851.

2 Chauffard, A., Laroche, G., and Grigaut, A. La cholestérimie à l'état normal et pathologique, Ann. de med. **8** 69-91 (Aug.) 1920, Le cycle de la cholestérine dans l'organisme, ibid. **8** 149-172 (Sept.) 1920, Les dépôts locaux de cholestérine: rapports entre la cholestérine circulante et la cholestérine fixée, ibid. **8** 321-334 (Nov.) 1920.

3 Burns, F. S. A Contribution to the Study of the Etiology of Xanthoma Multiplex, Arch. Dermat. & Syph. **2** 415-429 (Oct.) 1920.

4 Wile, U. J., Eckstein, H. C., and Curtis, A. C. Lipid Studies in Xanthoma, Arch. Dermat. & Syph. **19** 35-51 (Jan.) 1929.

but Boas and others⁵ stated the belief that xanthomas are associated with hypercholesterolemia at some stage during their development. In 1893, Torok⁶ recognized the familial tendency of tuberous xanthomas and made an extensive study of the literature concerning the various aspects of xanthomas. Since then, approximately thirty papers have reported tuberous xanthomas in 2 or more members of a family.

There has been some discord as to the genetic transmission of this supposed trait because of its sporadic occurrence within families involved. Levin and Sullivan⁷ stated that tuberous xanthomas are inherited as a recessive trait. They stated "The condition is transmitted as a recessive characteristic and may be inherited through either parent." This opinion on genetic transmission is not in agreement with the general consensus, which is that a trait transmitted as an autosomal recessive character must be through both parents. I have studied all the available case reports of familial tuberous xanthomas and have been unable to find data on any family in which xanthomas could be interpreted as having been transmitted by autosomal recessive factors. Thannhauser and Magendantz,⁸ Muller,⁹ Cockayne¹⁰ and other authors have stated the belief that tuberous xanthomas are transmitted as a dominant mendelian trait.

Basically, the inherited defect is one of lipid metabolism or, more specifically of cholesterol metabolism, the occurrence of xanthoma tuberosum, angina pectoris, arcus senilis, xanthelasma and atheroma is a complication or variation of the disease. This theory is substantiated by the case reports in the present paper. Muller,^{9b} Boas and others¹¹ Wile and Duemling¹² and others reported similar findings.

5 Boas, E. P., Parets, A. D., and Adlersberg, D. Hereditary Disturbance of Cholesterol Metabolism. A Factor in the Genesis of Atherosclerosis, *Am Heart J* **35** 611-622 (April) 1948.

6 Torok, L. De la nature des xanthomes avec quelques remarques critiques sur la notion des tumeurs, *Ann de dermat et syph* **4** 1109-1156, 1893.

7 Levin, A. L., and Sullivan, M. Familial Xanthoma. Report on Three of Five Siblings with Xanthoma Tuberosum Multiplex, *Arch Dermat & Syph* **33** 967-969 (June) 1936.

8 Thannhauser, S. J., and Magendantz, H. The Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of Twenty-Two Cases, *Ann Int Med* **11** 1662-1746 (March) 1938.

9 (a) Muller, C. Xanthomata, Hypercholesterolemia, Angina Pectoris, *Acta med Scandinav*, 1938, supp 89, pp 75-84, (b) Angina Pectoris in Hereditary Xanthomatosis, *Arch Int Med* **64** 675-700 (Oct) 1939.

10 Cockayne, E. A. Inherited Abnormalities of the Skin and the Appendages, New York, Oxford University Press, 1933.

11 Boas, Parets and Adlersberg⁵ Boas, E. P., and Adlersberg, D. Familial Hypercholesterolemia (Xanthomatosis) and Atherosclerosis, *J Mt Sinai Hosp* **12** 84-86 (May-June) 1945.

12 Wile, U. J., and Duemling, W. W. Familial Xanthoma, *Arch Dermat & Syph* **21** 642-647 (April) 1930.

Stecher and Hersh¹³ analyzed mathematically the reports of hereditary disturbances of cholesterol metabolism reported by Boas and his co-workers⁵ and stated "We are thus led to the conclusion that hypercholesterolemia is an autosomal dominant trait with complete or nearly complete penetrance"

Arcus senilis¹⁴ (arcus lipoides) and xanthelasma are frequently seen in patients with hypercholesterolemia. Montgomery and Osterberg¹⁵ stated that the histologic picture and the hyperlipemia in cases of xanthelasma strongly suggest that xanthelasma is an accompaniment of systemic disease and is simply a variation of one of the types of xanthoma. Barker¹⁶ and Montgomery¹⁷ reported cases of occlusive arterial disease of the lower extremities associated with hyperlipemia and xanthoma tuberosum. Literature on this subject is sparse.

There are many reports in the literature showing that xanthomatous lesions may occur on the heart valves and in other structures of the heart so as to hamper its efficiency greatly. As early as 1873, Fagge¹⁸ stated

The nature of the growth [xanthoma] appears to be a kind of universal atheromatous change and is essentially the same wherever it occurs. It will thus be seen that the condition is exactly parallel to that found in the early stages of atheromatous degeneration of the arteries.

But only during the last two decades has much emphasis been placed on the relationship of xanthoma tuberosum, hypercholesterolemia and coronary heart disease.

Torok⁹ (1893) reported cases in which death was due to xanthomatous changes in the cardiovascular system of patients with cutaneous xanthoma. In 1913, Anitschkow and Chalatow¹⁹ produced lesions which resembled the atherosclerotic plaques of the human being by

13 Stecher, R. M., and Hersh, A. H. Note on the Genetics of Hypercholesterolemia, *Science* **109** 61-62 (Jan 21) 1949.

14 Klatskin, G. Familial Xanthomatosis and Arcus Senilis, *Internat Clin* **3** 13-39 (Sept) 1941.

15 Montgomery, H., and Osterberg, A. E. Xanthomatosis. Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, *Arch Dermat & Syph* **37** 373-402 (March) 1938.

16 Barker, N. W. Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, *Ann Int Med* **12** 1891-1895 (May) 1939.

17 Montgomery, H. Xanthomatosis. A Systemic Disease, *Proc Staff Meet, Mayo Clin* **12** 641-644 (Oct 13) 1937.

18 Fagge, C. H. General Xanthelasma or Vitiligoidea, *Tr Path Soc London* **24** 242-250, 1872-1873.

19 Anitschkow, N., and Chalatow, S. Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, *Centralbl f allg Path u path Anat* **24** 1-9 (Jan 15) 1913.

feeding rabbits cholesterol That observation was confirmed by Bailey,²⁰ Leary²¹ and others Stocks²² stated that a conservative estimate of the incidence of atherosclerosis of the coronary arteries in patients with angina pectoris is 85 per cent

The physiologic role played by cholesterol in the human body is still poorly understood It is a constituent of all animal tissues, but the nature of its metabolism and synthesis remains unproved Montgomery and Osterberg,¹⁵ Thannhauser and Magendantz⁸ and Gubner and Ungerleider²³ recently reported detailed studies and quoted extensive literature concerning cholesterol and other lipid substances in relation to their clinical, histopathologic and chemical significance

Recent papers have reported a high incidence of disturbances in blood lipid metabolism in patients suffering from coronary heart disease Mjassnikow²⁴ reported on 16 patients with atherosclerosis, 12 of whom had angina pectoris The serum cholesterol level was elevated in all Davis and his co-workers²⁵ found that the levels for total cholesterol, free fatty acids and lipid phosphorus were higher among 59 patients with angina pectoris than in a comparable group of controls Twenty-two of the 28 young patients with disease of the coronary arteries reported on by Lerman and White²⁶ had serum cholesterol values above 250 mg per hundred cubic centimeters Boas and others,⁵ Steiner and Domanski,²⁷ Underdahl and Smith,²⁸ Yater and his associates²⁹ and many others reported similar findings Laliberté and Vachon³⁰ and

20 Bailey, C H Atheroma and Other Lesions Produced in Rabbits by Cholesterol Feeding, *J Exper Med* **23** 69-85 (Jan) 1916

21 Leary, T Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary) Atherosclerosis, *Arch Path* **17**:453-492 (April) 1934

22 Stocks, P, in Cowdry, E V Arteriosclerosis A Survey of the Problem, New York, The Macmillan Company, 1933, chap 7

23 Gubner, R, and Ungerleider, H E Arteriosclerosis A Statement of the Problem, *Am J Med* **6** 60-83 (Jan) 1949

24 Mjassnikow, A L Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, *Ztschr f klin Med* **102** 65-78, 1925

25 Davis, D, Stern, B, and Lesnick, G Lipid and Cholesterol Content of Blood of Patients with Angina Pectoris and Arteriosclerosis, *Ann Int Med* **11** 354-369 (Aug) 1937

26 Lerman, J, and White, P D Metabolic Changes in Young People with Coronary Heart Disease, *J Clin Investigation* **25** 914 (Nov) 1946

27 Steiner, A, and Domanski, B Serum Cholesterol Level in Coronary Arteriosclerosis, *Arch Int Med* **71** 397-402 (March) 1943

28 Underdahl, L O, and Smith, H L Coronary Artery Disease in Women Under the Age of Forty, *Proc Staff Meet, Mayo Clin* **22** 479-482 (Oct 15) 1947

29 Yater, W N, and others Coronary Artery Disease in Men Eighteen to Thirty-Nine Years of Age, *Am Heart J* **36** 481-526 (Oct) 1948

30 Laliberté, H, and Vachon, M Infarctus du myocarde et cholestérol (Rapport préliminaire), *Laval méd* **13** 294-302 (March) 1948

Welin³¹ reported on a total of 192 patients with myocardial infarction, most of whom had hypercholesteremia

In 1910, Arning³² reported xanthoma tuberosum in a mother and 4 of her 9 children. All 5 affected persons had heart disease. Similar reports have been made in the past, but not until recently have familial defects in the metabolism of the lipids been recognized as an important cause of heart disease. The reports of Lane and Goodman,³³ Montgomery and Osterberg,¹⁷ Muller¹⁰ and others have apparently brought about this recognition. Boas and others⁵ suggested that families with xanthoma may represent only the extremes of disturbed cholesterol metabolism and that many patients with apparently uncomplicated disease of the coronary arteries might fall into a similar pattern. Investigation into the problem has been greatly hampered because of the lack of opportunity to study families large enough to indicate the specific type of genetic transmission of the metabolic defect and, thus, to allow a

TABLE 1—*Cholesterol Values in a Patient with Coronary Arteriosclerosis*

Date	Total Serum Cholesterol, Mg /100 Cc	Comment
1/28/49	340	
2/ 7/49	340	
2/10/49	338	Sample obtained 24 hours after ingestion of 2 Gm cholesterol with 50 cc 20 per cent alcohol
2/14/49	318	
2/18/49	300	
2/25/49	168	
2/25/49	238	Sample obtained 4 hours after ingestion of 50 cc choline bicarbonate
2/26/49	224	Sample obtained 24 hours after ingestion of the choline

better understanding of it. Other difficulties encountered are in the quantitative determination of total lipids and serum cholesterol in affected persons. There is little deviation in the cholesterol level of normal persons, whereas a wide fluctuation is well known to exist in consecutive determinations in affected persons. Steiner and Domanski²⁷ showed that patients with coronary arteriosclerosis had much greater fluctuations in cholesterol levels from month to month than did controls. This has also been noted in my studies, the following case report is illustrative.

A woman of 31 had extremely large tuberous xanthomas over the heels, knees, back and dorsum of the hands (she was not a member of the family reported on later in this paper). The serum cholesterol values are listed in table 1.

31 Welin, G. Serum Cholesterol in Cardiac Infarctions, *Nord med* **37** 324-326 (Feb 13) 1948

32 Arning, E. Ein Fall von familiärer Xanthomatose, abstracted, *Arch f Dermat u Syph* **105** 290-291 (Oct 26) 1910

33 Lane, C G, and Goodman, J, Jr. Xanthoma Tuberosum. Report of Familial Occurrence with Probable Cardiac Lesions, *Arch Dermat & Syph* **32** 377-384 (Sept) 1935

During the period of observation, there were no changes in the patient's dietary habits or environment, but on February 25 there was a sudden drop of 50 per cent in the total serum cholesterol

Thus, a normal serum cholesterol level determined from a single blood sample does not necessarily exclude a person from the group having hypercholesteremia McGraw³⁴ stated the belief that determinations of blood cholesterol or blood lipids alone are of little value in the study of patients with xanthomatous lesions Samples should be obtained from patients in the fasting state and analyzed as soon as possible for total serum lipids and cholesterol The quantitative determinations of the various components of the blood lipids are of value, and the analysis of the relative amounts of these constituents may in the future lend much to a better understanding of this problem

REPORT ON FAMILY

Pedigrees of two families, members of which intermarried in one instance, are presented graphically in figure 1 There was a definite familial tendency toward heart disease in family B and complete absence of any type of heart disease in family A Both families were originally of Northern European stock They belonged to the same religious sect (Latter-Day Saints) and so lived rather similar lives Generations I and II of both families had migrated to the Rocky Mountains and helped to settle the communities in which they lived

Family A—I was able to obtain information concerning this family dating to 1743 It was impossible to ascertain the cause of death for those members living many years ago, but the age of death for the principal members shows the high incidence of longevity among them As will be noted, in family B the age of death was almost uniformly in the fifth or sixth decade of life, whereas several members of family A lived to be over 85 Information was exact as to the day and year of birth and death for nearly all persons, specific vital statistics were available for the following

I-1 This woman was born in 1802, the date of death was unknown She was delivered of 10 children (7 males and 3 females)

II-2 This man was born in 1799 and died at 77 His father was born in 1743, the date of his death is uncertain However, several siblings were known to be younger than subject I-2

II-1 The second wife of subject II-3 was born in 1847 and died at 73 She was delivered of 7 children (4 males and 3 females) Two male children were still living at the time of writing One was 89, the other 85

II-2 The third wife of subject II-3 was born in 1843 and died at 79 She was delivered of 5 children (4 males and 1 female) The male children died at the ages of 57, 72, 75 and 78, the daughter was still living at 81

34 McGraw, A B Juvenile Xanthoma Multiplex Case Report and Discussion of the Literature, *Am J Cancer* **18** 345-356 (June) 1933

II-3 This man was born in 1823 and died at 57

II-4 The first wife of subject II-3 was born in 1822 and died at 65 She had several brothers and sisters who lived to that age

III-1 to III-8 These subjects died at the following ages birth, 57, 11, 64, 22 (malaria ?), 38 (pneumonia), 30 (pneumonia) and 58

III-9 This man, born in 1861, died at 82 of cancer of the stomach

The descendants of the wives of subject II-3 numbered into the hundreds I was unable to find any history of a familial type of heart disease or of xanthoma in them except in the descendants of subject III-9, who married into family B.

Family B—I was able definitely to establish a high incidence of heart disease, xanthoma tuberosum, angina pectoris and hyperlipemia in five, and possibly six, generations of this family. Although both

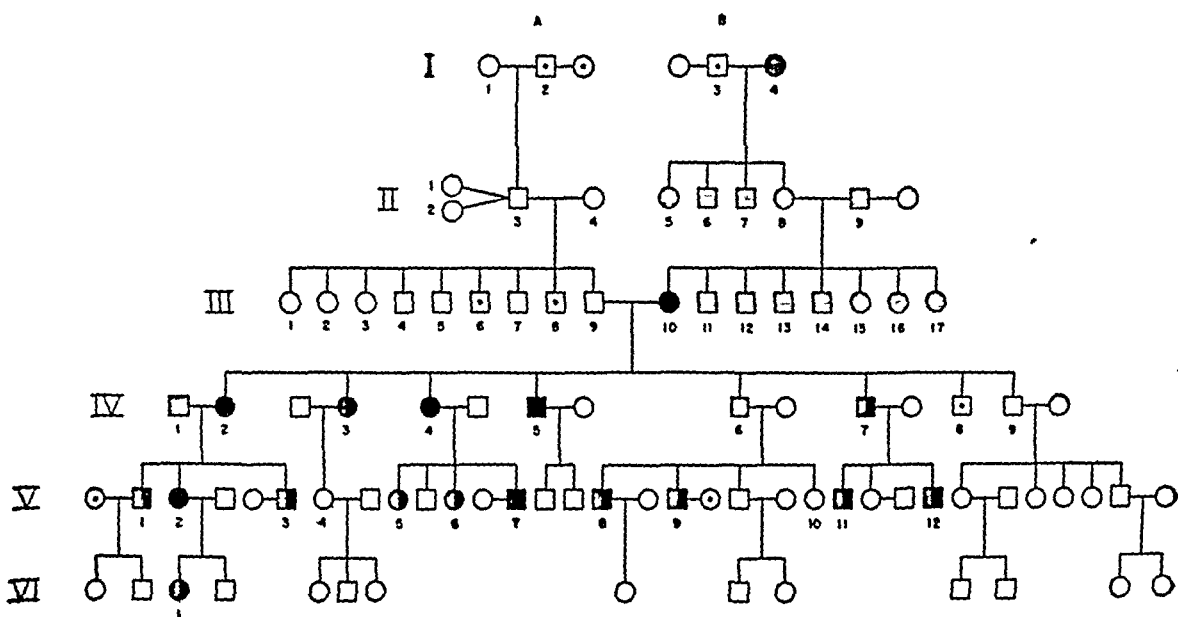


Fig 1—Pedigree chart of two unrelated families, members of which intermarried in one instance. Family A was normal in all respects, family B showed a high incidence of heart disease, xanthomas and hyperlipemia. The square symbols designate males, and the round symbols, females. The symbols with black dots represent normal persons, and the plain figures indicate persons not examined or for whom no history could be obtained. The solid black symbols designate persons with xanthoma tuberosum, angina pectoris and hyperlipemia occurring together (Additional material in the text concerns subjects III-10, IV-3 and IV-5). The half-solid symbols represent subjects with hyperlipemia.

family A and family B lived in an area endemic for rheumatic heart disease, apparently few persons, if any, in either family became afflicted with the disease. I found only 1 instance (that of subject I-3) of a person's living past 65 in this family. According to the history obtained, all persons in the first three generations of this family except subject I-3 died of heart disease. The following data were obtained:

Generation I I-3 It was estimated by persons in generation IV that the subject died in his eighties (cause unknown).

I-4 This woman was presumably the original person in this pedigree transmitting the trait. It is believed that she died of heart disease in "midlife."

Generation II II-5 This woman died suddenly of "heart disease" in "midlife."

II-6 This man died of "heart disease" at a "young age."

II-7 This man died of "heart disease" in his fifties.

II-8 This woman died suddenly at 65 after a heart attack.

II-9 This man died of heart trouble in his sixties. Several siblings of his second wife were known to have heart disease.

There were several additional siblings of subjects I-3 and I-4 who are not graphically represented in the pedigree chart because of lack of information concerning them. It was well known in the community that most of these siblings and many of their descendants had heart disease. Local physicians would tell members of generation III that they were afflicted with "one of those [family name] hearts."

Generation III III-10 The subject died at 57 of cancer of the stomach. She had xanthoma tuberosum of the achilles tendons, arcus senilis and a long history of angina pectoris.

III-11 The subject died suddenly at 45 of heart disease. He suffered from several attacks of angina pectoris.

III-12 This man died at 60 after many years of heart trouble.

III-13 This man died suddenly at 46 after severe pain in the chest. The history revealed several attacks of angina pectoris.

III-14 This man died at 51 after many years of heart trouble.

III-15 This subject died at 51 of heart disease. She had "dropsy" for some time before death.

III-16 The subject died suddenly at 50 of a heart attack. She suffered from angina pectoris.

III-17 The subject died at 50 of heart disease. She had "dropsy" before death.

There were 4 additional siblings in generation III who are not represented graphically in the pedigree chart because of lack of information concerning them. Subjects III-11 to III-17 had over 250 descendants, most of whom were available for study. However, I was unable to undertake a task of such scope.

Generation IV IV-1 This man died suddenly of coronary occlusion at 47. One brother also died of coronary occlusion, at 48.

IV-2 The patient, a woman of 62, was first seen at the Stanford University Hospitals because of a history of severe pain of several years' duration in the lower portion of the back. The condition was diagnosed as lumbosacral arthritis, for which a spinal fusion was performed on Jan 31, 1949. The studies concerning xanthomas, disturbances in lipid metabolism and angina pectoris were made because of interest in this subject and were incidental to the presenting orthopedic problem.

The patient had four attacks of severe substernal pain in twelve years, the last occurring on March 28. The administration of glyceryl trinitrate completely eliminated the pain in the chest. The patient often became dyspneic on exertion. The tuberous xanthomas of the achilles tendons were first noted when she was 37. Xanthelasma and arcus senilis had been present "only for the past few years."

The blood pressure was 130 systolic and 80 diastolic. Arcus senilis and xanthelasma of the right upper eye lid were noted. The heart was not enlarged, there were no thrills or murmurs, and the rhythm was regular. The peripheral blood vessels were soft. Lesions of xanthoma tuberosum (6 mm in diameter) were located on the extensor tendons of the index fingers, fusiform tuberous xanthomas 10 by 4.5 cm, were located within the distal portion of the achilles tendons.

Blood values were as follows: red blood cells, 5,050,000, hemoglobin, 15.5 Gm per hundred cubic centimeters, packed cell volume, 38 per cent, sedimentation rate,

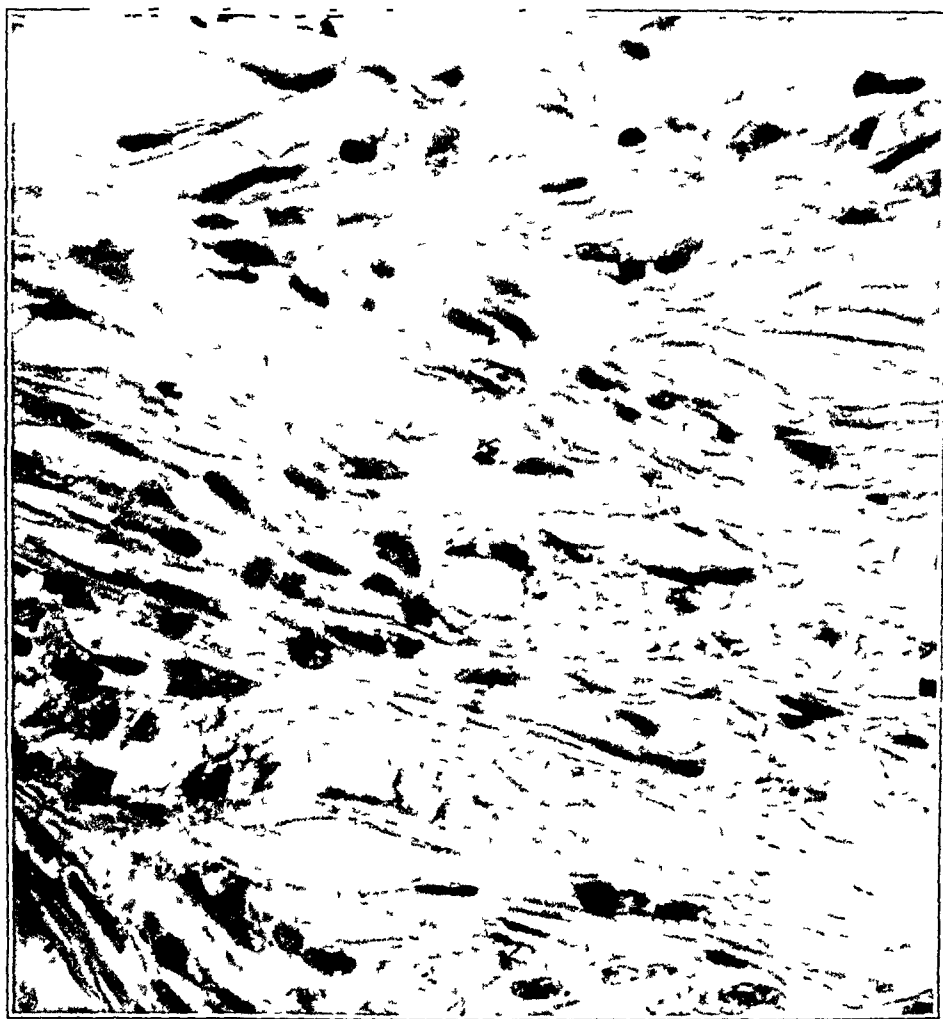


Fig 2—Photomicrograph of biopsy specimen of lesion of xanthoma tuberosum from left achilles tendon of subject IV-2. Dense bands of collagen are prominent, and there are numerous fibroblasts. Occasional polymorphonuclear leukocytes lie outside the capillary walls. A number of large, pale-staining foam cells are present. The diagnosis was xanthoma and foreign body reaction of the achilles tendon.

30 mm in one hour, and white blood cells, 9,500 (polymorphonuclear leukocytes 58 per cent, lymphocytes 42 per cent). The urine was normal.

An electrocardiogram made on January 31 showed left axis deviation but was otherwise normal. The Wassermann and Hinton reactions were negative. Biopsy of a mass on the left achilles tendon, diagnosed as a xanthoma (fibroxanthoma), gave a foreign body reaction (fig 2). Blood chemistry values are given in table 2.

IV-3 The patient was a woman of 58. She had had severe attacks of angina pectoris for the past twenty years, glyceryl trinitrate eliminated pain in the chest. At the age of 55, she had had a sudden, excruciating pain in the chest, electrocardiograms reportedly suggested myocardial damage at that time. Large tuberous xanthomas were noted on the extensor tendons of the hands and on the achilles tendons, and xanthelasma and arcus senilis were present. The onset of the tuberous xanthomas of the achilles tendons had been in the patient's early twenties. The xanthomas were occasionally painful. When she was 30, a thyroidectomy was performed at the Mayo Clinic. On examination, the heart was found to be normal, the basal metabolic rate was +38, and no lipid studies were made. The following is a summary of information concerning the "swellings" on the achilles tendons, which existed at that time.

"The tendons were found to be uniformly enlarged and rather spindle shaped, and there was a deposit of yellowish, almost orange-colored fatty tissue between the fiber and the tendons. About all that was performed at operation was the removal of enough of this tissue, which included both the fat and the tendon, to reduce them to normal size. To remove all the fatty tissue would have

TABLE 2—Summary of Blood Chemistry Values in Subject IV-2

Date	Total Serum Cholesterol, Mg /100 Cc	Total Serum Lipids, Mg /100 Cc	Comment
1/30/49	640		Patient received 500 cc whole blood 1/31/49
2/4/49	615		Patient placed on low fat and cholesterol diet
2/10/49	512		
2/14/49	576	1,566	Control specimen obtained for choline investigation
	1,300	1,593	Sample obtained 4 hr after ingestion of 50 cc choline bicarbonate
2/15/49	946	1,513	Sample obtained 24 hr after ingestion of choline
4/25/49	713	1,749	Eleven weeks since patient placed on diet

necessitated removing the entire tendons for a distance of probably 2 or 3 inches [5 or 7.5 cm]. The pathologic reports on the tissue removed at operation indicated fibrolipoma with fairly extensive fatty infiltration and degeneration of the heel cord. Back of it all, there was rather an unusual family history."

It is interesting to note that the lesions of the heel cords at the time of writing were much larger than before the operation. At the time of the operation, the lesion was diffuse throughout the entire tendon. Ollerenshaw,³⁵ Lewis³⁶ and others reported that a tendon may be diffusely infiltrated by a xanthoma.

IV-4 The patient was a woman of 56. The blood pressure was 130 systolic and 80 diastolic. There were xanthomas on the extensor tendons of the hands and fusiform tuberous xanthomas (9.5 by 4 cm) of the achilles tendons. No arcus senilis was noted, there was xanthelasma bilaterally. Several attacks of "crushing" pain in the chest had occurred, and the patient had had dyspnea for the "past few years." She had been "anemic for some time." The xanthomas of the achilles tendons developed at about the age of 7, at times, they had become very painful.

35 Ollerenshaw, R. Giant-Celled Tumours of Tendon Associated with Xanthelasma, *Brit J Surg* 10 466-468 (April) 1923.

36 Lewis, D. Tumors of the Tendon Sheaths, *Surg, Gynec & Obst* 59 344-349 (Sept) 1934.

Blood chemistry values on March 28, 1949 were as follows total serum cholesterol, 276 mg, and total serum lipids, 1,970 mg per hundred cubic centimeters

IV-5 The subject was a man of 47 Tuberous xanthomas were observed on the extensor tendons of the hands and on the achilles tendons, there was no xanthelasma or arcus senilis, and no history of heart disease Blood chemistry values on March 24, 1949 were as follows total serum cholesterol, 444 mg, and total serum lipids, 1,375 mg per hundred cubic centimeters

IV-6 The patient, a man, died at 52 He had cancer of the stomach, but the family was told by their physician that he died of heart disease and not of the cancer On several occasions, he had severe substernal pains

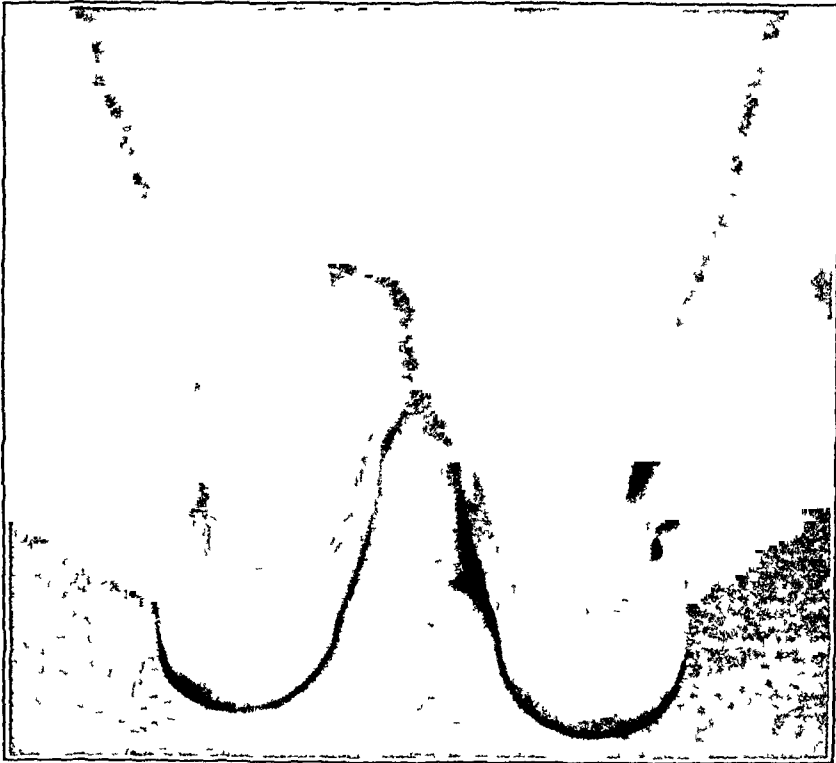


Fig 3—Posterior view of lesions of xanthoma tuberosum on achilles tendons of subject V-2

IV-7 The subject was a man of 52 The blood pressure was 120 systolic and 70 diastolic No xanthomas were observed, and there was no arcus senilis and no history of dyspnea or angina pectoris Blood chemistry values on March 28, 1949 were as follows total serum cholesterol, 154 mg, and total serum lipids, 1,300 mg per hundred cubic centimeters

IV-8 This boy died at the age of 5 years of sarcoma of the stomach

IV-9 The subject was a male of 51 No further information was available at the time of writing

Generation V V-1 This male subject was 36 The blood pressure was 124 systolic and 76 diastolic No xanthomas were observed, and there was no arcus lipoides or history of heart disease Blood chemistry values were as follows on March 28, 1949 total serum cholesterol, 194 mg, and total serum lipids, 1,325 mg per hundred cubic centimeters

V-2 The patient was a woman of 30 The blood pressure was 128 systolic and 82 diastolic, fusiform tuberos xanthomas of the achilles tendons measuring approximately 10.5 by 4.5 cm, had been present since the age of 21 (figs 3 and 4) There was no xanthelasma or arcus lipoides On March 14, 1949 the patient had a sudden severe pain in the chest which necessitated hospitalization for five days The pain was completely relieved by glyceryl trinitrate Electrocardiograms were normal at that time Studies of the blood, made on February 1, yielded the following data red blood cells, 4,500,000, hemoglobin, 13.5 Gm per hundred cubic centimeters, white blood cells, 8,000, differential count, normal, sedimentation rate, 7 mm in one hour, and packed cell volume, 39 per cent Blood chemistry values are listed in table 3

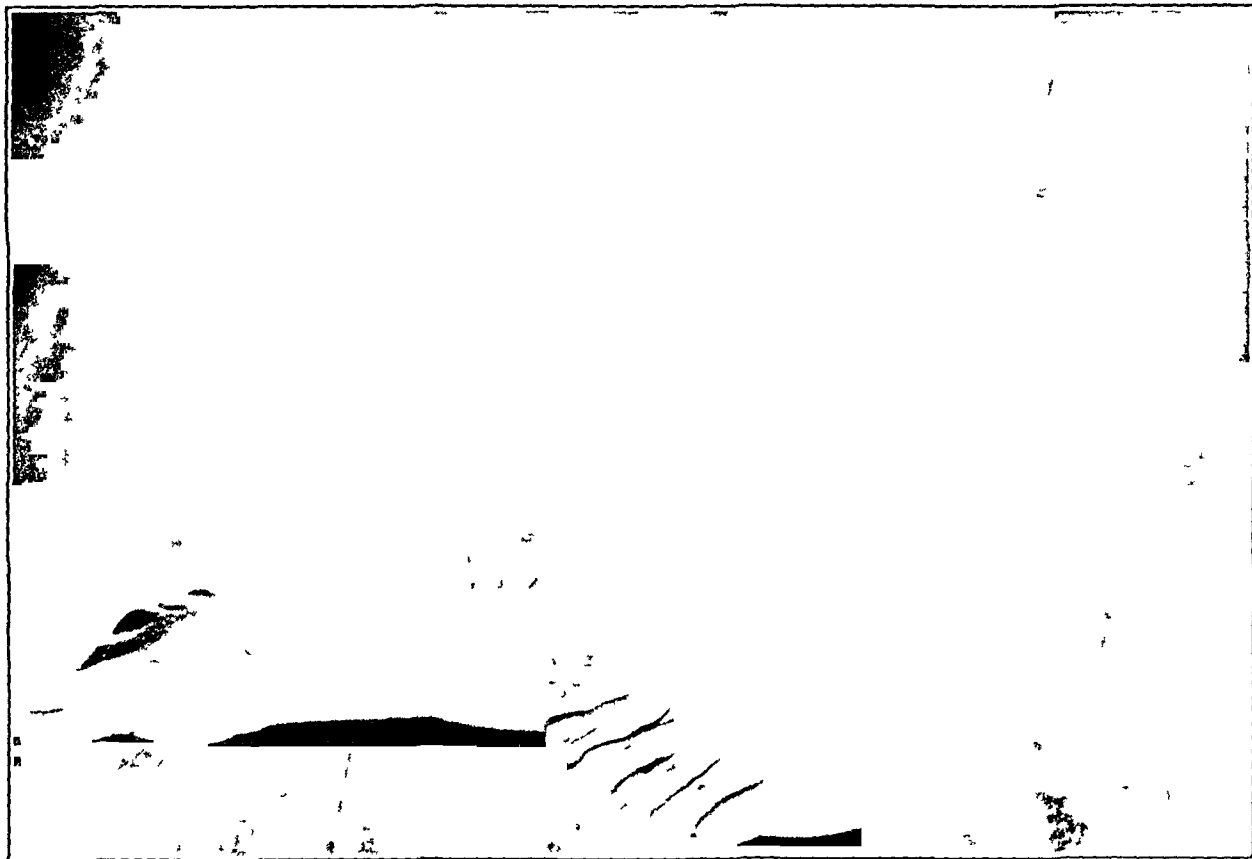


Fig 4—Lateral view of lesions of xanthoma tuberosum on achilles tendon of subject V-2

V-3 The subject was a man of 34 The blood pressure was 122 systolic and 78 diastolic No xanthomas were observed, there was no arcus lipoides or history of heart disease Studies of the blood on Feb 1, 1949 showed the following red blood cells, 4,800,000, hemoglobin, 14.2 Gm per hundred cubic centimeters, white blood cells, 8,900, differential count, normal, sedimentation rate, 9 mm in one hour, and packed cell volume, 40 per cent Blood chemistry values were 325 mg per hundred cubic centimeters for total serum cholesterol and 35 mg for blood urea

V-4 No information was available at the time of writing, other than that the subject was a female

V-5 This subject was a girl of 16 The blood pressure was 116 systolic and 86 diastolic On palpation, the achilles tendons were noted to be much thicker than one would expect in a girl of this age She stated that there was occasionally

"something like a pain" sensation in them. No xanthomas were observed on the hands, elbows or eyelids. There was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 217 mg, and total serum lipids, 2,410 mg per hundred cubic centimeters.

V-6 The subject was a woman of 27. The blood pressure was 120 systolic and 80 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 136 mg, and total serum lipids, 2,312 mg per hundred cubic centimeters.

TABLE 3—*Summary of Blood Chemistry Values in Subject V-2*

Date	Total Serum Cholesterol, Mg /100 Cc	Total Serum Lipids, Mg /100 Cc	Comment
8/16/48	448		Patient placed on low fat and cholesterol diet
2/ 1/49	327		Blood urea, 29 mg /100 cc
2/ 5/49	645		
2/ 9/49	401	1,251	Sample obtained 24 hours after ingestion of 50 cc choline bicarbonate

TABLE 4—*Summary of Blood Chemistry Determinations for 16 Persons in Family B*

Case	Sex	Age, Years	Total Serum Cholesterol, Mg /100 Cc	Total Serum Lipids, Mg /100 Cc	Comment
IV 2	F	62	512-1,300*	1,513-1,749*	Xanthomas, angina pectoris
IV 4	F	56	276	1,970	Xanthomas, angina pectoris
IV 5	M	47	444	1,375	Xanthomas
IV 7	M	52	154	1,300	
V 1	M	36	194	1,325	
V 2	F	30	401-645*	1,231	Xanthomas, angina pectoris
V 3	M	34	325		Blood urea, 35 mg /100 cc
V 5	F	16	217	2,410	
V 6	F	27	136	2,312	
V 7	M	30	148	1,835	
V 8	M	30	313	802	
V 9	M	29	201-262*	765-1,028*	
V 10	F	25	175	544	
V 11	M	20	169	1,662	
V 12	M	15	115	1,295	
VI 1	F	9	373		

* Range of various samples

V-7 The subject was a man of 30. The blood pressure was 102 systolic and 80 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 148 mg, and total serum lipids, 1,835 mg per hundred cubic centimeters.

V-8 The subject was a man of 30. The blood pressure was 128 systolic and 70 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on Feb 14, 1949: total serum cholesterol, 313 mg, and total serum lipids, 802 mg per hundred cubic centimeters.

V-9 The subject was a man of 29. The blood pressure was 138 systolic and 86 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on April 5

1949 total serum cholesterol, 201 mg, and total serum lipids, 765 mg per hundred cubic centimeters On April 25, the values had risen to 262 and 1,028 mg, respectively

V-10 The subject was a woman of 25 The blood pressure was 120 systolic and 72 diastolic No xanthomas were observed, and there was no arcus lipoides or history of heart disease Blood chemistry values were as follows on April 25, 1949 total serum cholesterol, 175 mg, and total serum lipids, 544 mg per hundred cubic centimeters

V-11 The subject was a youth of 20 The blood pressure was 122 systolic and 80 diastolic No xanthomas were observed, and there was no arcus lipoides or history of heart disease Blood chemistry values were as follows on March 28, 1949 total serum cholesterol, 169 mg, and total serum lipids, 1,662 mg per hundred cubic centimeters

V-12 The subject was a boy of 15 The blood pressure was 112 systolic and 76 diastolic No xanthomas were observed, and there was no arcus lipoides or history of heart disease Blood chemistry values were as follows total serum cholesterol, 145 mg, and total serum lipids, 1,295 mg per hundred cubic centimeters

Generation VI VI-1 The subject was a girl of 9, no xanthomas were observed, and there was no arcus lipoides or history of heart disease The value for total serum cholesterol on Feb 5, 1949 was 373 mg per hundred cubic centimeters

The information concerning both family A and family B was obtained principally from IV-2, IV-4 and IV-7 at different interviews These people were active in genealogic work, which explains the exactness and scope of the information I examined the genealogic records of the families

Generations IV, V and VI are referred to as belonging to family B in comment on them

COMMENT

Blood lipid studies showed that 15 of the 16 persons examined in family B had pronounced elevations of the level for total serum lipids, total serum cholesterol or both No serum lipid studies were made on any members of family A The blood chemistry determinations were done in duplicate under similar conditions by an experienced technician Each value in the reported present article is an average of the two independent determinations made on that sample Blood specimens from subjects IV-2 and V-2 were also analyzed in two different laboratories, the results were comparable to those obtained by the usual technician The total serum cholesterol was determined by the method of Sperry and Brand³⁷ and the total lipids by the method of Wilson and Hanner³⁸ The upper limits for "normal" values used were

37 Sperry, W M, and Brand, F C The Colorimetric Determination of Cholesterol, *J Biol Chem* **150** 315-324 (Oct) 1943

38 Wilson, W R, and Hanner, J P Changes of Total Lipid and Iodine Number of Blood Fat in Alimentary Lipemia, *J Biol Chem* **106** 323-330 (Aug) 1934

approximately 275 mg per hundred cubic centimeters for total serum cholesterol and 800 mg for total serum lipids

Tuberous Xanthoma—Six persons (III-10, IV-2, IV-3, IV-4, IV-5 and V-2) had tuberous xanthomas of the achilles tendons. Five of the 6 had a history of angina pectoris, and 4 had arcus senilis. It appears that at least in this family arcus senilis associated with disturbances in lipid metabolism does not develop until about the sixth decade of life.

Trauma has been mentioned as an etiologic agent in the formation of tuberous xanthoma, but this was not found to be so in family B or in the literature. The persons having tuberous xanthoma in this family claimed never to have had serious injuries to the achilles tendons. If the theory of trauma were valid, one would expect more men than women to have these lesions because of the greater hazards present in their occupational environment. Grenaud³⁹ compiled the reports of cases of xanthoma to 1927 and stated that the sex incidence was equal and that the time of appearance of the xanthoma was between birth and 40. The greatest number of occurrences were in patients aged from 3 to 6 years.

Swanson⁴⁰ stated that in cases of familial xanthoma cutaneous lesions may appear, or, more commonly, there may be a derangement of cholesterol metabolism giving rise to gallstones and atheromas. There is no history of members of either family having diabetes mellitus, jaundice (subject III-5 may have had it), disease of the gallbladder, disease of the kidneys, hypothyroidism or obesity.

Heart Disease—Five members (II-5, II-8, III-11, III-13 and III-16) of family B died suddenly of heart disease. Three of these experienced severe pain in the chest before death. Four members (IV-2, IV-3, IV-4 and V-2) of family B living at the time of writing suffer from angina pectoris, and 2 deceased members (III-10 and IV-6) are known to have had angina pectoris. Three members (III-12, III-14 and III-15) died of a "slow kind" of heart disease in the sixth decade of life. Of the 4 remaining members represented in the pedigree chart as having heart disease, all died before the seventh decade of life. It is known that they had heart disease, but I was unable to obtain any specific information which would allow me to classify the type of cardiovascular disease. Two persons (II-9 and IV-1) who married into family B had heart disease.

The average age of death in family A was 72.2, whereas that in family B was 52.8. I have not included the subjects in family A who died young of infectious diseases, and I have excluded subjects I-3 and IV-8 because of certainty that they did not die of heart disease. Both

39 Grenaud, M. Les xanthomes familiaux, *Monde méd* **37** 725-731 (Aug. 1) 1927.

40 Swanson, J. C. Familial Xanthomatosis. *Brit J Dermat* **55** 289-293 (Dec.) 1943.

family A and family B lived in the same rural community. Their environment was the same, and their diets were similar (their activities, diet and environment were controlled to a great extent through their religious teachings). Thus, in two families living under very similar conditions, the average life expectancy was twenty years longer for one than for the other.

The inherited disturbances in lipid metabolism occurring in family B were, in general, of a benign nature until about midlife. At that time, the cardiovascular system seemed to be involved to such an extent that most of the members succumbed to what was apparently coronary heart disease. Similar observations were made in Norway by Muller.³⁹ I was unable to determine whether the patients who died of the "slow type" of heart disease had myocardial or valvular involvement due to xanthomatous deposits, as reported by Torok,⁶ Low,⁴¹ Cook and others,⁴² Lenzen and Knauss,⁴³ and others, or had rheumatic heart disease.

I took blood pressure readings on 16 members of this family. None of them had hypertension, however, all but subject V-10 had hyperlipemia. Much investigation has been done in regard to the effect of elevated blood lipid levels (especially hypercholesteremia) on blood vessels and on their role in the formation of atherosclerosis. Two recent papers reviewed this problem in detail.⁴⁴

Cancer —Three members of family B (III-10, IV-6 and IV-8) died of cancer of the stomach. Much work has been done relating to cholesterol as a cause of, or a significant factor in, cancer. A few authors have reported cancer of the gastrointestinal system in patients with xanthomas,⁴⁵ but these reports are so uncommon in relation to the large number of reports of patients with xanthomatous lesions that one is led to believe that there is nothing in common between xanthomas and cancer.

Diet —Much controversy has arisen over the probable effects of a diet high in cholesterol in the development of atherosclerosis. The

41 Low, R. C. Xanthoma Tuberosum Multiplex, with Lesions in Heart and Tendon Sheaths, *Brit J Dermat* **22** 109-118 (April) 1910.

42 Cook, C. D., Smith, H. L., Giesen, E. W., and Berdz, G. L. Xanthoma Tuberosum, Aortic Stenosis, Coronary Sclerosis and Angina Pectoris, *Am J Dis Child* **73** 326-333 (March) 1947.

43 Lenzen, G., and Knauss, K. Ueber Xanthoma multiplex planum, tuberosum, mollusciforme, *Virchows Arch f path Anat* **116** 85-104 (April) 1889.

44 Gubner, R., and Ungerleider, H. E. Cholesterol Metabolism and Arteriosclerosis, Combined Staff Clinics, *Am J Med* **6** 103-124 (Jan.) 1949, footnote 23.

45 Weidman, F. D., and Schaffer, H. W. Xanthoma of the Skin and Larynx Associated with Carcinoma of the Stomach and a Regressive Xanthoma of the Pons, *Arch Dermat & Syph* **35** 767-814 (May) 1937. Weidman F. D., and Boston, L. N. Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of an Intercurrent Zoster. Adenocarcinoma of the Ampulla of Vater at Necropsy, *Arch Int Med* **59** 793-822 (May) 1937.

advocates of a low cholesterol diet, designed to prevent the development of arteriosclerosis, have based their opinions on the experimental production of atherosclerosis in the rabbit, the chicken and the dog. They have also pointed out that people living in areas where poor nutrition is prevalent supposedly have a low incidence of atherosclerosis. Gardner and Gainsborough⁴⁶ stated that there is no connection between the amount of sterol ingested and the cholesterol levels of the plasma during digestion. Chaikoff and his associates⁴⁷, Turner and Steiner⁴⁸ and others were unable to produce any significant change in the serum cholesterol levels of "normal" persons by feeding them diets high in cholesterol. Steiner⁴⁹ reported on 35 patients given a high fat diet supplemented with 20 Gm of cholesterol. Blood specimens were taken at 8 a m (fasting state), 10 a m, noon and 4 p m, and at 8 a m the following day. The results showed that little or no change in the serum cholesterol level occurred during the period, regardless of the ingestion of a large amount of cholesterol.

Subject IV-2 was placed on a low cholesterol and fat diet on Feb 4, 1949. At that time she had a total serum cholesterol level of 615 mg per hundred cubic centimeters. Blood specimens eleven weeks later showed a total serum cholesterol level of 713 mg, a rise of nearly 100 mg (she had consumed no fats or cholesterol for thirty-six hours, and had eaten nothing for eighteen hours previous to the drawing of the second specimen). Subject V-2 was also placed on a restricted cholesterol diet for nearly six months, with no change whatsoever in the total serum cholesterol level. There were no changes in the size of the tuberous xanthomas in either of these subjects during their dietary periods. It seems apparent that diet has little or no effect on the serum lipid levels in normal persons or in those with a hereditary type of hyperlipemia (hypercholesteremia).

Hereditry—I have shown that six generations of family B had or had had heart disease and/or hyperlipemia. The inherited trait was a type of endogenous metabolic defect giving rise to high levels of serum lipids. The elevated blood lipid level in itself was unimportant clinically as evidenced by the complete absence of symptoms in 11 members of the family having hyperlipemia. However, all 11 were under 36.

46 Gardner, J. A., and Gainsborough, H. Studies on the Cholesterol Content of Normal Human Plasma, *Biochem J* **22** 1048-1056, 1928.

47 Chaikoff, I. L., McGavack, T., and Kaplan, A. The Blood Lipids in the Postabsorptive State and After the Ingestion of Fat in Normal Human Subjects and in a Case of Disseminated Cutaneous Xanthomata, *J Clin Investigation* **13** 1-13 (Jan) 1934.

48 Turner, K. B., and Steiner, A. A Long Term Study of the Variation of Serum Cholesterol in Man, *J Clin Investigation* **18** 45-49 (Jan) 1939.

49 Steiner, A., in discussion on Cholesterol Metabolism and Arteriosclerosis, ⁴⁷ pp 117-120.

Xanthoma tuberosum, xanthelasma, arcus senilis, angina pectoris (presumably associated with coronary sclerosis) and possibly xanthomatous involvement of the myocardium and valves were complications arising from prolonged hyperlipemia in this family. In general, these complications arise in the fifth and sixth decades of life with the exception of xanthoma tuberosum, which usually occurs at an earlier age.

Fliegelman and his associates⁵⁰ stated the belief that the heterozygous alleles cause only hypercholesteremia, whereas the homozygous dominant condition is manifested not only as hypercholesteremia but also in the appearance of tuberous xanthomas and in cardiovascular changes. I have not found this to be so in my studies or elsewhere in the literature.⁵¹

Hyperlipemia in this family was transmitted as a simple autosomal dominant trait with complete penetrance.

Treatment—The treatment of this condition is entirely symptomatic at the time of this report. Theoretically, some medicinal substance may be given to keep the serum cholesterol and other serum lipids at a normal level and thus eliminate the complications of prolonged hyperlipemia, but as yet no substance has been found which can achieve this for long periods. I gave choline bicarbonate to several members of family B for this purpose, but the results were inconclusive.

SUMMARY

A survey is presented on a family in which 15 members had hyperlipemia, 6 had xanthoma tuberosum and 18 had a history suggesting disease of the coronary arteries. Two factors were noted:

1. A disturbance in lipid metabolism was the basic inherited defect.
2. Hyperlipemia (hypercholesteremia) was inherited as a simple autosomal dominant trait.

The pertinent literature is reviewed.

ADDENDUM

After the completion of this study, a history of heart disease was obtained for 21 additional descendants of subjects I-3 and I-4. The ages of the subjects range from 7 to 61 years, 6 were under the age of 20. Over 200 members of this family remain to be studied.

Alvin J. Cox Jr., M.D., Windsor C. Cutting, M.D., and Donald E. King, M.D., gave technical advice in this study, and Miss Helen O'Connell, B.A., performed many of the serum lipid determinations.

⁵⁰ Fliegelman, M. T., Wilkinson, C. F., and Hand, E. A. Genetics of Xanthoma Tuberosum Multiplex, *Arch. Dermat. & Syph.* **58** 409-429 (Oct.) 1948.

⁵¹ Boas and others⁵ Bloom, D.; Kaufman, S. R., and Stevens, R. A. Hereditary Xanthomatosis, *Arch. Dermat. & Syph.* **45** 1-18 (Jan.) 1942.

Book Reviews

Hematology By Cyrus C Sturgis, M.D. Price, \$12.50 Pp 915 Springfield, Ill Charles C Thomas, 1948

Dr Sturgis' new text of hematology is an extremely personal book. In every section the material is presented in an intimate and informal manner which is much more reminiscent of a ward walk than a handbook. Hematology is a discipline which is greatly complicated by variations in nomenclature and terminology. Frequently this complexity leads to particularism and to a tendency for the students to concentrate on details and numbers and to neglect the broad view of the subject. It is also a discipline which has attracted clinical pathologists rather than internists, so that not infrequently attention has been directed mainly to technologic matters rather than to the patient as a sick person. The broad clinical experience and background of the author are apparent throughout this book. The periodical literature of hematology is very extensive, and much of it is contradictory and controversial. During the past eleven years Dr Sturgis and his associates have prepared the annual reviews of hematology for the *ARCHIVES*. With this comprehensive bibliography at his disposal the author has been able to document his textbook in detail. The reviews have been objective, as a rule, and have presented all the recent work in the field. In his textbook, Dr Sturgis has been much more critical and has attempted a just evaluation of the contributions that he cites.

The book is primarily clinical, and there are no chapters devoted to technical methods. All the major problems of clinical hematology are discussed, and the reviewer feels that the space assigned to each subject is adequate. A thorough historical review precedes the description of each of the principle blood dyscrasias. In a field which is developing as rapidly as hematology it is inevitable that some of the contemporary work will not be discussed. It is unfortunate that the recent studies of the Rh factor and of the use of exsanguination transfusion in the treatment of erythroblastosis fetalis could not have been included. Likewise, many readers would appreciate a presentation of Sturgis' opinions on the use of the nitrogen mustards and a more detailed discussion and evaluation of the employment of radioisotopes in the treatment of blood diseases.

The format of the book is pleasing, and the reviewer is heartily in favor of the practice of placing bibliographic references at the bottom of the pages on which they occur. The illustrations are generally good, and the tables and graphs are clear and adequate. This textbook is recommended for advanced students and for physicians interested in hematology. The mature clinical judgments, the excellent historical notes and the carefully selected bibliography should win a place for this book in the library of every hematologist.

Blood Clotting and Allied Problems Transactions of the First Conference February 16-17, 1948, New York. Sponsored by the Josiah Macy Jr Foundation, New York. Edited by Joseph E Flynn. Price, \$3.25 Pp 179 New York Josiah Macy Jr Foundation, 1948

Here is the first of a series of reports by groups of outstanding investigators in specified fields which are sure to become indispensable aids to true students of medicine. The careful selection of the contributors and the fundamental nature of their presentation will appeal to those readers who are seeking authentic, practical information. For instance, "Blood Clotting and Hemostasis" is presented by L. B. Jaques, of Canada, "Fibrinolytic Enzymes" by Tage Astrup of Copenhagen,

"Initiation and Acceleration Factors in Thrombosis" by K M Brinkhaus, "Protein Equilibrium Reactions in the Blood-Clotting Mechanism" by W H Seegers and A G Ware and "Dicoumarol and the Estimation of Prothrombin" by Karl Link, and there are others of equal importance. The discussion of the papers by the other members of the group adds great interest and clarification.

In an extensive appendix the exact procedures for prothrombin determinations which are carried out in the various laboratories of several of the participants are given. The contributors to this section include, among others, Quick, Tocontins, Seegers, Barker, of the Mayo Clinic, and Brambel, of Toronto.

This report will be eagerly received by laboratory directors, clinicians and medical investigators who are anxious to increase their understanding of this difficult subject and the accuracy of their laboratory technics.

Le fond d'oeil des hypertendus et des cyanoses. By Daniel Routier, M D
Pp 100, with 232 illustrations. Paris: Masson & Cie, Editeurs Libraires de l'Academie de Medecine, 1947.

The author, who is a cardiologist, presents in black and white 232 photographs of the fundus of the eye, each picture accompanied with brief notes regarding the clinical condition of the patient and pointing out the noteworthy changes in the retina and retinal vessels. He used a Nordenson camera at exposures of one tenth to one twenty fifth of a second, with about the success that others have had with this somewhat unsatisfactory instrument, some of his photographs being good and others only fair.

In the first chapter he describes and illustrates the normal fundus, and in the second he presents the generally recognized vascular and retinal changes of hypertensive disease. Some would take exception to his emphasis on tortuosity of retinal vessels as evidence of hypertension. He stresses the significance of local spasms of the retinal arterioles and notes that they may persist for many months, and he rightly points to these changes and to the small exudates as having greater significance than have some of the gross changes which are more readily seen.

A chapter on interpretation deals with the origin of retinal edema and of various types of exudates and is an excellent summary of present opinion on the subject. A final chapter illustrates cases of congenital and acquired cyanosis.

Psychiatry in General Practice. By Melvin W Thorner, M D, D Sc. Price, \$8. Pp 659. Philadelphia: W B Saunders Company, 1948.

In the past a wide gap has separated the psychiatrist and the rest of the medical profession. This is unfortunate because, in practically every instance, the family physician sees the patient first and, in the long run, is required to treat more mentally ill patients in the stage when treatment short of shock therapy may be effective than the psychiatrist. Dr Thorner's book, "Psychiatry in General Practice," as stated in his preface, "is an attempt to lift psychiatry out of the realm of terra incognita for those whose primary efforts are spent in other fields."

Only by removing the aura of mystery from the practice of psychiatry, can psychiatry be rendered a useful tool in the hands of those who deal with the greatest number of psychiatric patients."

One cannot help but agree with Dr C C Burlingame in his foreword when he points out that "to an astonishing degree, the author of this book has overcome the psychiatric language barrier." The clear presentation of psychiatric problems, with short, illustrative case histories and without long, abstract discussions full of the catch words and theoretic claptrap of so much of the present day writing

on this subject, is, indeed, refreshing. The book is cheerfully recommended to the uninitiated who up to this time—with some justification—have regarded psychiatrists and their specialty with some suspicion and alarm.

Mayo Clinic Diet Manual By the Committee on Dietetics of the Mayo Clinic
Price, \$4 Pp 329 Philadelphia W B Saunders Company, 1940

This is an excellent manual. The material was originally prepared for use in teaching and in planning the diets of patients at the Mayo Clinic, it was put into its present printed form in answer to requests from physicians and from other institutions. It represents the convergent trend but not necessarily unanimity of opinion. Because of the rapid headway being made in the science of nutrition, frequent revised printings are contemplated.

The manual consists of a comprehensive series of dietary tables with a minimum of explanatory notes. It is well planned for easy reference, and the physician can find in it a detailed outline of practically any dietary regimen he may need. It is concise, and the foods are prescribed in household measures.

A few of the dietary patterns appear to the reviewer to be faulty in minor details, such as the relatively large proportion of cream in the milk-cream mixture used for peptic ulcer (1:1) and the conservatism with which protein is prescribed, as well as the liberal amount of fat allowed, in diseases of the liver. On the whole, however, these diets will appeal to the physician and to the nutritionist as being eminently suitable. The pragmatic test, based on the theory that practical results are the sole test of truth, has been applied. These diets have all been evaluated on the results of clinical trial. The teacher of nutrition as well as the physician in practice will find the manual a valuable aid.

Textbook of the Rheumatic Diseases Edited by W S C Copeman, O B E, M D, F R C P Price, \$12.50 Pp 612, with 351 illustrations Baltimore The Williams & Wilkins Company, 1948

This beautifully printed and profusely illustrated book is a cooperative effort on the part of some two dozen British physicians to cover comprehensively the subject of the "rheumatic diseases." Introductory chapters on history, anatomy and physiology of pain and anatomy and physiology of joints give some idea of the thoroughness of the approach. The various rheumatic diseases are then taken up systematically, with final sections on such specific topics as the radiology of rheumatic disease, radiotherapy, physiotherapy and psychiatric aspects. Each section is followed by a bibliography, many of them comprehensive. Most of the discussions are adequate, although that on rheumatic fever, comprising only 10 in a book of some 600 pages, seems perhaps too brief, however, further material on this most important "disease" is given later in the volume. The illustrations, some in color, and the reproductions of roentgenograms are outstanding. The book is certainly a landmark on the subject, and our British colleagues have done themselves proud in producing such an outstanding compilation.

Fundamentals of Pulmonary Tuberculosis By Edward W Hayes, M D Price, \$9.50 Pp 480, with 79 illustrations Springfield, Ill Charles C Thomas, Publisher, 1949

"The purpose of this book is to present in as few concise chapters as possible the fundamentals pertaining to the cause, the prevention, the diagnosis, the treatment and the control of tuberculosis." These aims are achieved in twenty-six chapters, written by twenty-seven experts in the field of tuberculosis.

In spite of the large number of contributors to this book, the editor has kept repetitious discussion to a minimum

Although certain chapters inevitably stand out in a volume of this type, most of the fundamental aspects of tuberculosis are satisfactorily discussed. Due to the progress that is being made from month to month in the antibacterial therapy of tuberculosis, it would be impossible for the chapter on this subject to contain the latest developments. However, the earlier discoveries are reviewed, and the proper use of streptomycin is described in detail.

The book has been prepared for "the medical student, the practicing physician and the medical teacher," and each of them will find it to be a satisfactory review of the various aspects of pulmonary tuberculosis.

Shock and Allied Forms of Failure of the Circulation By H. A. Davis, M.D., C.M., F.A.C.S. Price, \$12. Pp. 608, with 55 illustrations. New York: Grune & Stratton, Inc., 1949.

This volume is an ideal book in regard to size, binding, format and printing. For an initial work it appears to be singularly free from typographical errors. In spite of these excellent physical aspects the book is difficult to read, owing to the almost encyclopedic character of the subject material. The author has made an extensive review of the literature on both experimental and clinical work pertaining to shock and to shocklike states. In addition, he presents a considerable amount of data based on his own researches and observations. Although the review of the literature is not complete on some minor aspects of the subject, a compilation of all the references cited at the end of each chapter would probably represent the most complete index of articles on acute circulatory failure in existence. The book is a valuable addition to medical literature and should prove to be especially useful to investigators working on problems related to acute failure of the circulation.

Roentgen Studies of the Lungs and Heart A series of lectures delivered at the center for continuation study. Edited by Leo G. Rigler, M.D. Price, \$7. Pp. 216, with 98 illustrations. Minneapolis: University of Minnesota Press, 1948.

This series of lectures delivered at the University of Minnesota by Westermarck summarizes his methods for study of the heart and lungs. The use of controlled intrapulmonary respiratory pressure, positive and negative, for the study of pulmonary lesions is particularly interesting. The early diagnosis of bronchogenic carcinoma, the identification of localized as well as generalized emphysema and the discussion of pulmonary embolism and infarction and of roentgen cinematography to observe hemodynamics are included and should prove to be of value to roentgenologists, physiologists and cardiologists. The text is accompanied by many illustrations, but unfortunately the accompanying legends are relatively incomplete and poorly written. Since the illustrations are so numerous, more detailed legends and labeling would have been of considerable value to the average reader.

Neutron Effects on Animals By the Staff of the Biochemical Research Foundation (Dr. Ellice McDonald, Director). Price, \$3. Pp. 198. Baltimore: The Williams and Wilkins Company, 1947.

Nearly a score of investigators contributed to this volume, the chapters of which resemble separate publications such as might be found in almost any periodical dealing with the medical sciences. The material consists of detailed

reports concerning a great variety of findings after irradiation with neutrons, the methods and doses employed are described fully. Experimental animals included dogs, rabbits, rats, mice and chickens, plants and micro-organisms were also used. The effects of irradiation under consideration range from those on mortality, body weight, growth and "clinical" behavior to those on formed elements and sedimentation rate of the blood, ordinary "blood chemistry," gastric juice, enzymes, histologic appearances, neoplasm induction and electrophoresis of plasma and homogenized bone marrow.

Child Psychiatry By Leo Kanner, M.D. Enlarged second edition. Price, \$8.50. Pp 776. Springfield, Ill. Charles C Thomas, 1949.

Dr Kanner's work on child psychiatry at Johns Hopkins Hospital is too well known to require much introduction. The handsome volume just issued embodies his latest and carefully considered views on the subject. No aspect of child psychiatry has been left untouched. The general background is developed, the relation of physical ills to mental reactions is discussed and finally the psychiatric disturbances in the stricter sense are taken up. Although the book is a large one, the subject is so great that one almost has a feeling of sketchiness here and there, some of the sections on therapy especially seem almost too brief. Dr Kanner (and this cannot be said of all psychiatrists) writes vividly and intelligibly, his book no doubt remains the standard text on this subject.

Annual Review of Physiology (Volume XI), 1949 By Victor E. Hall. Price, \$6.00. Pp 643. Stanford University, Calif. Annual Reviews, Inc., 1949.

Included in this book are reviews of work in the fields of developmental physiology, neurophysiology, physiologic psychology, radiation and pharmacology, and of work on the reproductive system, the metabolic functions of the endocrine system, the liver, the digestive system, the hearing, the vision, the muscles, the lymphatic system, the heart, the peripheral circulation, the respiration, the kidneys, hematopoiesis and permeability. Each reviewer has attempted to present the pertinent, rather than all, recent contributions related to his subject. Nevertheless, over 4,300 references are included. The volume is a well organized and concise survey. It offers the scientifically trained reader a valuable and practical means of keeping abreast of basic physiologic investigation.

Histopathology of the Peripheral and Central Nervous Systems By George B. Hassin, M.D. Third edition. Price, \$8.50. Pp 612, with 325 illustrations. Hamilton, Ill. The Hamilton Press, 1948.

Dr Hassin's book first appeared in 1933, and the present edition (1948) is the third one. The author has turned publisher in this case, and the work appears under his own imprint. It is well printed on fine paper, and the numerous illustrations are excellently reproduced. Dr Hassin is well known as an authority on neurohistology, and wherever one turns in this book he finds a precise and clear discussion. There are extensive bibliographies, and the book will continue as in the past to be a valuable text and reference book.

INDEX TO VOLUME 84

Book Reviews are grouped together and are indexed under that heading in alphabetical order under the letter B

Abdomen See also Gastrointestinal Tract, Peritoneum, etc
 abdominal epilepsy, 514
 adhesions, intra-abdominal, 519
 clinical significance of bacteroides, 605
 Distension See Abdomen, pressure in
 pain, 513
 pressure in, hysterical type of nongaseous abdominal bloating, 217
 war wounds and abdominal surgery, 515
Abnormalities and Deformities See also under names of organs and regions, as Heart, etc
 congenital anomalies, 513
Abscess See under names of organs and regions as Abdomen, etc
Addison's Anemia See Anemia, pernicious
Adhesions, intra-abdominal, 519
Adolescence See Puberty
Aerosols, Therapy See Respiratory Tract, diseases
Agglutinins and Agglutination, symptoms attributable to cold hemagglutination, report of 2 cases, 523
Air Passages See Respiratory Tract
Allergy See Asthma
Alvarez, W C Hysterical type of nongaseous abdominal bloating, 217
Alvord, R M Coronary heart disease and xanthoma tuberosum associated with hereditary hyperlipemia, study of 30 affected persons in family, 1002
Amebiasis, 464
American Medical Association, third annual clinical session of, 836
Ames, F Reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders, criticism of methods, 396
Amromin, G D Dissecting aneurysms of aorta, 558
Anaphylaxis and Allergy See Asthma
Ancylostomiasis See Hookworm Infection
Anemia associated with cirrhosis of liver, 958
Bartonella See under Bartonella
 pernicious, in early adolescence, report of case in girl of 14, 445
Aneurysm, aortic, dissecting aneurysms of aorta, 558
 spontaneous rupture of syphilitic saccular aneurysms of ascending aorta into pericardial cavity, with hemopericardium, report of sudden death in 29 cases, 540
Angina, pectoris, concepts of myocardial ischemia, 711
Anomalies See Abnormalities and Deformities
Anorexia Nervosa See Appetite
Antibiotics, Therapy See Colon, diseases, Pneumonia, etc
Antimony and Antimony Compounds See Schistosomiasis
Anus See also Rectum
 and rectum, 505
 anorectal surgery, 506
 congenital anomalies, 505
 fissures and fistulas, 505
 hemorrhoids, 506
 Pruritus See Pruritus and
 war wounds, 506
Aorta Aneurysm See Aneurysm, aortic
 syphilis, spontaneous rupture of syphilitic saccular aneurysms of ascending aorta into pericardial cavity, with hemopericardium, report of sudden death in 29 cases, 540

Aortitis, Syphilitic See Aorta, syphilis
Appendicitis, 470 See also Appendix
Appendix, diverticulosis of, 473
Intussusception See Intussusception
 mucocoele of, 473
 roentgenologic examination of, 470
 tumors, 473
Appetite and olfactory acuity, 509
 disorders, anorexia nervosa, 509
Applebaum, I L Clinical syndrome of occlusion of posterior inferior cerebellar artery, report of 3 cases, 431
Archer, B H Clinical and biochemical study of remissions in nonspecific arthritis, report of case, 361
Armed Forces Personnel See Military Medicine, Naval Medicine, Veterans, etc
Arteries See also Aneurysm, Blood pressure, Blood vessels, Embolism, Periarthritis, Thrombosis, etc
 cerebellar, clinical syndrome of occlusion of posterior inferior cerebellar artery, report of 3 cases, 431
 Coronary See Coronary Vessels
 Hypertension See Blood pressure, high
Arthritis, nonspecific, clinical and biochemical study of remissions in, report of case, 361
Aschoff-Klinge Nodule See Rheumatic Fever
Asthma, aerosol and micronized ephedrine and penicillin therapy of diseases of lower respiratory tract, treatment of bronchitis, bronchiectasis and intrinsic asthma, 389
Atom Bomb See Atomic Energy
Atomic Energy, hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
Atrophy See under names of diseases, organs and regions, as Liver, etc
Aureomycin, Therapy See Pneumonia
Autopsies, Osler's original autopsy books, 7
Awards, urology award, 836
Bacteremia, clinical significance of bacterioides, 605
Bacteria See Pneumococci, etc
 Dysentery See Dysentery
 Mycobacteria See Tuberculosis
 Salmonella See Salmonella
 Shigella See Dysentery
Bacteroides, clinical significance of, 605
Barbital and Barbital Derivatives, barbiturate poisoning, report of 3 cases, 379
Bartonella Bacilliformis See Oroya Fever
Bateman, J C Symptoms attributable to cold hemagglutination, report of 2 cases, 523
Bean, W B Excerpts from Osler, mosaic of bedside aphorisms and writings, 72
Beigelman, P M Clinical significance of bacterioides, 605
Blerring, W L Day with Dr Osler in Oxford, 143
Bilharziasis See Schistosomiasis
Biliary Tract See Liver
Biographies, biography of William Osler, 1-198
Biology, international symposium on high altitude biology, 836
Bjørneboe, M Pathology of subchronic atrophy of liver, comparison with Laennec's cirrhosis, 933
Blood See also Anemia, Erythrocytes
 cholesterol, coronary heart disease and xanthoma tuberosum associated with hereditary hyperlipemia, study of 30 affected persons in family, 1002
Circulation See also Arteries Heart, etc
 circulation, reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders, criticism of methods 396

Blood—Continued

- Diseases See Anemia etc
 fats and lipoids, coronary heart disease and xanthoma tuberosum associated with hereditary hyperlipemia, study of 30 affected persons in family, 1002
 hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
 Platelets See also Purpura
 platelets, role in thromboembolism 667
 pressure, high, intestinal lesions in malignant hypertension, 351
 pressure, high, pathogenesis of renal lesions in Bright's disease, 159
 pressure, high, sympathectomy and splanchnicectomy, 331
 Vessels See also Arteries, Periarthritis etc
 vessels reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders, criticism of methods 396
 vessels vascular disease 351
 Blumer G Iocular side of Osler 34
 Body Mind and Body See Mind, body and mind
 Bones See also under names of bones
 Diseases See Osteomyelitis
 marrow, sternal marrow in patients with metastatic cancer, 891
 multiple myeloma with new bone formation 976

BOOK REVIEWS

- A M A Interns Manual, 844
 Anales de la cátedra de clínica medica, E S Wazzel 665
 Annual Review of Physiology (Volume XI) 1949 V E Hall, 1201
 Archives of Internal Medicine Epidemiology of Hemolytic Streptococcus, A F Coburn and D C Young, 663
 Atlas of Electrocardiography, W Dressler and H Roesler, 666
 Blood Clotting and Allied Problems, J L Flynn 1020
 Cardiac Catheterization in Congenital Heart Disease A Cournaud J S Baldwin and A Himmelstein, 843
 Cardiovascular Disease in General Practice T East 840
 Child Psychiatry, L Kanner, 1021
 Clinical Aspects and Treatment of Surgical Infections T L Melenev, 842
 Clinical Auscultation of Heart, S A Levine and W P Harvey 661
 Coronary Artery Disease, E P Boys and N F Boas 660
 Coronary Heart Disease, A C Frustene 813
 Diabetic Manual for Doctor and Patient L P Joslin 521
 Diagnosis of Viral and Rickettsial Infections T L Horsfall Jr 663
 Digestive Tract in Roentgenology I Buckstein 942
 Female Sex Endocrinology, C H Birnberg, 666
 Food Poisoning, G M Dack 666
 Fundamentals of Pulmonary Tuberculosis, E W Hayes, 1022
 George R Minot Symposium of Hematology, W Dameshek and I H L Taylor 664
 Hematology C C Sturgis 1020
 Hemolysis and Related Phenomena, L Ponder 838
 Heredity in Human Leukemia and Its Relation to Cancer, A Videback, 521
 Histopathology of Peripheral and Central Nervous Systems, G B Hassin 1021
 History of Heart and Circulation, T A Willis and T J Dry 360
 Introduction to Cardiology, G Bourne 841
 Investigations into Development of Pituitary and Hereditary Anterior Pituitary Dwarfism in Mice F Francis 357
 Le fond de l'oeil des hypertendus et des cyanoses D Routier 1021

BOOK REVIEWS—Continued

- Literature on Streptomycin 1911-1918 S A Waksman, 843
 Manual of Medical Emergencies, S C Cullen and E G Gross, 665
 Mayo Clinic Diet Manual, Committee on Dietetics of Mayo Clinic 1022
 Medical Etymology, O H Perry Pepper, 662
 More than Armies Story of Edward H Cary MD, B Mooney 811
 Mycoses and Practical Mycology, N Gohar, 842
 Neutron Effects on Animals, Staff of Biochemical Research Foundation 1023
 Oral and Dental Diagnosis, K H Thoma, 664
 Pathology W A D Anderson 378
 Posttraumatic Epilepsy A L Walker 843
 Practical Aspects of Thyroid Disease, G Crile Jr 358
 Present Concepts of Rehabilitation in Tuberculosis, N C Klefer 666
 Psychiatry in General Practice, M W Thorner, 1021
 Rh Blood Groups and Their Clinical Effects, P L Mollison A F Maurant and R R Race 810
 Roentgen Studies of Lungs and Heart L G Rigler 1023
 Shock and Allied Forms of Failure of Circulation H A Davis 1023
 Studies of Chronic Pyelonephritis, F Raaschou, 667
 Symposium on Cardiovascular Diseases Especially Hypertension, Medical Clinics of North America, 662
 Symposium on Diseases of Skin Medical Clinics of North America 661
 Symposium on Treatment of Long-Term Illness Medical Clinics of North America 811
 Synopsis of Pediatrics, J Zahorsky assisted by T S Zahorsky 818
 Textbook of Rheumatic Diseases, W S C Copeman 1022
 Thyroid Enlargement and Other Changes Related to Mineral Content of Drinking Water (with Note on Götter Prophylaxis), M M Murray, J A Ryle B W Simpson and D C Wilson 379
 Treatment of Malignant Disease by Radium and X-Rays Being Practice of Radiotherapy, R Paterson, 521
 Tuberculosis in Childhood, H F Macauley 357
 Twentieth Century Speech and Voice Correction, I Froeschels, 357
 Uses of Penicillin and Streptomycin, C S Kiefer 813
 Vitamin A Requirement of Human Adults An Experimental Study of Vitamin A Deprivation in Man A Report of Vitamin A Sub-Committee of Accessory Food Factors Committee, E M Hume and H A Krebs 839
- Books, manual on international exchange of publications 520
 Osler's original autopsy books 7
 Bouillaud's Disease See Rheumatic Fever
 Bowels See Intestines
 Boylston G A Ulcer of pyloric ring report of 20 cases 532
 Brawley, R W Q Fever in veterans hospital 917
 Bright's Disease See Nephritis
 Bronchial Dilatation See Bronchiectasis
 Diseases See Bronchiectasis, Bronchitis
 Bronchiectasis, aerosol and micronized ephedrine and penicillin therapy of diseases of lower respiratory tract, treatment of bronchitis bronchiectasis and intrinsic asthma, 389
 Bronchitis, aerosol and micronized ephedrine and penicillin therapy of diseases of lower respiratory tract treatment of bronchitis bronchiectasis and intrinsic asthma 389

- Bruce, R A Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
- Buser, I W Gastroenterology, review of literature from July 1947 to July 1948, 321, 449
- Cancer See also Sarcoma, and under names of organs and regions, as Intestines, etc
 carcinoma of colon, 494
 carcinomatous metastases, 518
 chronic ulcerative colitis and carcinoma, 293
 sternal marrow in patients with metastatic cancer, 891
- Carcinoma See Cancer
- Cardiovascular Diseases See Arteries, Heart
 System See Arteries, Blood vessels, Heart, etc
- Carrion's Disease See Oroya Fever
- Cathartics, sodium carboxymethylcellulose laxative effects in clinical use, 475
- Catheterization See Heart, diseases
- Chapman, D W Intravenous catheterization of heart in suspected congenital heart disease, report of 72 cases, 640
- Chemotherapy See under names of diseases as Asthma, Bronchiectasis, Bronchitis, etc
- Cheskin, L J Clinical syndrome of occlusion of posterior inferior cerebellar artery, report of 3 cases, 431
- Cholesterol in Blood See Blood, cholesterol
- Choline and Choline Derivatives, excretion of choline in urine of diabetic patients, 730
- Christian, H A Osler, recollections of undergraduate medical student at Johns Hopkins, 77
- Circulation See Blood, circulation
- Circulatory System See Blood, circulation, Heart
- Cirrhosis See under Liver
- Cisneros, F Myocardial infarction, observations on 100 patients who survived up to 6 years, 632
 Survival after recent myocardial infarction, 305
- Cold hemagglutination, symptoms attributable to, report of 2 cases, 523
- Cole, R Dr Osler, scientist and teacher, 54
- Colitis, ulcerative, 483
 ulcerative, chronic ulcerative colitis and carcinoma, 293
- Collins, H S Aureomycin therapy of nonpneumococcal and nontuberculous bacterial pulmonary infections, 875
 Aureomycin treatment of pneumococcal pneumonia clinical and laboratory study on 33 patients, 857
- Colon See Gastrointestinal Tract, Intestines
 anatomic studies of, 474
 colostomy, 503
 dilatation, megacolon, 480
 diverticulosis and diverticulitis, 478
 endometriosis, 490
 diseases, sulfonamide and antibiotic drugs in 491
 functional disorders of, 482
 Inflammation See Colitis
 microcolon, 482
 miscellaneous conditions of, 491
 output of fat and nitrogen, 475
 perforation, 491
 physiologic studies of, 474
 polyps and other tumors, 492
 proctosigmoidoscopy, 476
 radiation injury, 490
 roentgenologic examination of sigmoid, 476
 sodium carboxymethylcellulose, laxative effects in clinical use, 475
 studies on removal of gas from colon by oxygen inhalation 475
 tuberculosis of, 489
 volvulus 477
- Colostomy 503
- Communicable Diseases See Meningitis
 Syphilis, etc
- Congress See Societies
- Convulsions See Epilepsy
- Coronary Vessels, concepts of myocardial ischemia, 711
 traumatic coronary thrombosis with myocardial infarction, postmortem study, 261
- Cough, tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases 845
- Covner, A H Motor manifestations of herpes zoster, report of case of associated permanent paralysis of phrenic nerve, 907
- Csaky, T Z Excretion of choline in urine of diabetic patients, 730
- Cullen, T S The gay of heart 41
- Cyanosis, defect of ventricular septum, summary of 12 cases and review of literature 798
- Cysts See under names of organs and regions, as Duodenum, Intestines, Perineum, etc
- D'Angio, C J Multiple myeloma with new bone formation 976
- Davison, W C Sir William Osler, reminiscences 110
- Diabetes Mellitus, development of porphyria in, report of 3 cases, 965
 excretion of choline in urine of diabetic patients 730
 multiple hemorrhagic sarcoma and diabetes mellitus, review of series, with report of 2 cases, 738
- Diarrhea See also Dysentery
 diagnostic measures 450
 parasitic and diarrheal diseases, 450
 Tropical See Sprue
- Digestive System See Gastrointestinal Tract, Intestines, Stomach, etc
 foods and dyspepsia, 509
- Diverticula See Appendix, Colon, Duodenum
- Dock, G Dr Osler's use of time, 51
- Dragstedt, L R Gastroscopic and histologic appearance of gastric mucosa before and after vagotomy for peptic ulcer, 199
- Duff, I F Medical aspects of submarine warfare, human factor as reflected in war patrol reports, 246
- Duodenum, arteriomesenteric occlusion 333
 benign and malignant tumors, 334
 congenital defects, 332
 cysts, 333
 diverticula, 333
 diverticula, including Meckel's diverticulum, 337
 duodenitis, 333
 miscellaneous disorders, 333
 motility, 332
 removal of foreign bodies from, 333
 Ulcer See Peptic Ulcer
- Dysentery, Amebic See Amebiasis
 bacillary, 455
 miscellaneous observations on, 458
- Dyspepsia See Digestive System, diseases
- Earle, D M Intravenous catheterization of heart in suspected congenital heart disease, report on 72 cases, 640
- Education, postgraduate course in psychiatry and neurology at University of California Medical School, 356
 postgraduate courses on physics in radiation therapy at University of California, 355
- Ellis, A W M Pathogenesis of renal lesions in Bright's disease, 159
- Embolism, pulmonary, relation to peripheral thrombosis 410
 role of blood platelets in thromboembolism, 667
- Emerson, E B Tussive syncope observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
- Endocarditis, pathogenesis of renal lesions in Bright's disease 159
- Endometriosis as cause of obstruction of intestine 345
 of umbilicus 518

- Engel G Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
- Enteritis See Colitis, Diarrhea, Dysentery, Intestines, diseases, Gastrointestinal Tract, etc
- Enterostomy See Gastroenterostomy
- Eosinophilia, hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
- Ephedrine and Ephedrine Derivatives, Therapy See Respiratory Tract, diseases
- Epilation See Hair, removal
- Epilepsy, abdominal, 514
Laryngeal See Vertigo
- Erythrocytes, hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
- Extremities, Paralysis See also Poliomyelitis, paralysis, familial, periodic paralysis, report on 2 families, with observations on pathogenesis of syndrome 419
- Fat See Lipoids
- Feces fat in, steatorrhea and sprue 342
- Feeding, intravenous, total intravenous alimentation 509
- Felsen, J Chronic ulcerative colitis and carcinoma 293
- Fever, Rheumatic See Rheumatic Fever
- Ferrucous See Oroya Fever
- Films, revised edition of motion pictures reviews, 355
- Finland M Aureomycin therapy of non-pneumococcal and nontuberculous bacterial pulmonary infections, 875
Aureomycin treatment of pneumococcal pneumonia, clinical and laboratory studies on 33 patients, 857
- Fissure, Anal See Anus
- Fistula and fissures of anus 505
- Food See also Nutrition, etc
and dyspepsia, 509
poisoning, 451
- Fowler W M Pernicious anemia in early adolescence, report of case in girl of 14 445
- Fulton J F William Osler humanist 119
- Futcher, T B Dr Osler's renal stones, 40
- Gastric Ulcer See Peptic Ulcer
- Gastroenteritis See Food, poisoning, Gastrointestinal Tract
- Gastroenterology, review of literature from July 1947 to July 1948, 321 449
- Gastroenterostomy, leakage from enterostomy, 351
- Gastrointestinal Tract See also Colon, Digestive System, Intestines, Rectum, Stomach, etc
and poliomyelitis virus 459
anemia in gastrointestinal disease, 512
congenital anomalies, 513
diagnosis of gastrointestinal disease 512
epidemic gastroenteritis, 451
gastroenteritis in children, 451
gastrointestinal parasites, 460
incidence of gastrointestinal disease, 512
miscellaneous gastrointestinal subjects, 509
olfactory acuity and appetite, 509
psychosomatic factors in gastrointestinal disease 510
- Genitourinary Tract, clinical significance of bacteroides, 605
- Glossodynia See Tongue
- Glycosuria See Diabetes Mellitus
- Gocke, T M Aureomycin therapy of non-pneumococcal and nontuberculous bacterial pulmonary infections 875
Aureomycin treatment of pneumococcal pneumonia, clinical and laboratory studies on 33 patients, 857
- Goetz R H Reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders criticism of methods, 396
- Goldstein, P Spontaneous rupture of syphilitic saccular aneurysms of ascending aorta into pericardial cavity with hemopericardium, report of sudden death in 29 cases 540
- Goodman, B Role of blood platelets in thromboembolism, 667
- Greenfield, I Barbiturate poisoning, report of 3 cases, 379
- Gugle, L J Intravenous catheterization of heart in suspected congenital heart disease, report of 72 cases, 610
- Gwyn N B Medical arena in Toronto of Osler's early days in study of medicine, 2
- Hair, removal, hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
- Halpern, S L Motor manifestations of herpes zoster, report of case of associated permanent paralysis of phrenic nerve 907
- Hamilton, H E Pernicious anemia in early adolescence, report of case in girl of 11, 445
- Heart See also Blood, circulation
abnormalities defect of ventricular septum, summary of 12 cases and review of literature, 793
concepts of myocardial ischemia, 711
Diseases See also Endocarditis etc
diseases, coronary heart disease and rathoma tuberosum associated with hereditary hyperlipemia, study of 30 affected persons in family, 1002
diseases, intravenous catheterization in suspected congenital heart disease, report of 72 cases 610
infarction, myocardial infarction, observations on 100 patients who survived up to 6 years 632
infarction, traumatic coronary thrombosis with myocardial infarction, postmortem study 261
survival after recent myocardial infarction 305
- Heat reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders, criticism of methods 396
- Hecht H H Concepts of myocardial ischemia, 711
- Heine-Medin Disease See Poliomyelitis
- Hemagglutination See Agglutinins and Agglutination
- Hematology See Blood
- Hemopericardium See Pericardium, hemorrhage
- Hemopoietic System, Diseases See Anemia etc
- Hemorrhoids 506
- Hepatitis See Hepatitis, infectious
infectious, hepatitis and its sequelae, including development of portal cirrhosis, observations on 100 cases, 782
- Hernia 515
- Herpes zoster motor manifestations of report of case of associated permanent paralysis of phrenic nerve 907
- Herrick, J B William Osler, personal note, 46
- Huang, K W Anemia associated with cirrhosis of liver, 958
- Hookworm Infection, 461
- Hospitals, Q fever in veterans' hospital, 917
- Howard, R P William Osler, 'potent ferment' at McGill, 12
- Huggins, R A Intravenous catheterization of heart in suspected congenital heart disease report of 72 cases 640
- Humor, ocular side of Osler, 34
- Humphreys, E M Gastroscopic and histologic appearance of gastric mucosa before and after vagotomy for peptic ulcer, 199
- Hurlbut, W B Multiple hemorrhagic sarcoma and diabetes mellitus, review of series, with report of 2 cases 738
- Hypercholesterolemia See Blood, cholesterol

- Hyperlipemia See Blood, fats and lipoids
Hypertension See Blood pressure, high
- Icterus See Jaundice
Infantile Paralysis See Poliomyelitis
Infarction See under Heart
Infection See also Bacteremia, and under names of bacteria, as Pneumococci, etc
aureomycin therapy of nonpneumococcal and nontuberculous bacterial pulmonary infections, 875
Infectious Diseases See Infection, Meningitis, etc
Injections See Nutrition, Intravenous
Intestines See also Colon, Duodenum, Gastrointestinal Tract, Rectum
acute jejunitis, 340
benign and malignant tumors of, 353
congenital atresia of, 338
Diseases See also Diarrhea, Dysentery diseases, intestinal lipodystrophy (Whipple's disease), 345
diseases, regional enteritis, 338
diverticula, including Meckel's diverticulum, 337
endometriosis as cause of obstruction of, 345
enteric cyst, 338
flora, effect of oral streptomycin on, 459
gas, 336
hernia, 338
histological study of participation of intestinal epithelium, reticuloendothelial system and lymphatics in iron absorption and transport, 344
intubation, 350
Intussusception See Intussusception
leakage from enterostomy, 351
lesions in malignant hypertension, 351
motility, 334
nonspecific ulcers, 340
obstruction, 347
obstruction, phytobezoar in gastric stump, report of case and discussion of therapy, 824
perforation, traumatic resection and foreign bodies, 352
redundant postoperative segments, 351
roentgenologic examination of small bowel, 337
scleroderma with gastrointestinal involvement, 351
small intestine, 334
tuberculosis of, 340
viability of strangulated bowel, 349
Intravenous Feeding See Injections, Intravenous
Intussusception of appendix, 473
of intestine, 346
Iron, histological study of participation of intestinal epithelium, reticuloendothelial system and lymphatics in iron absorption and transport, 344
Ishibashi, K Hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
Itching See Pruritis
- Japan and Japanese, hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
Jaundice, clinical and biochemical study of remissions in nonspecific arthritis, report of case, 361
hepatitis and its sequelae, including development of portal cirrhosis, observations on 100 cases, 782
Jejunum See Intestines
Johns Hopkins Medical School, Osler, recollections of undergraduate medical student at Johns Hopkins, 77
Joints, Diseases See Arthritis
Journals See Periodicals
- Kaposi's Sarcoma See Sarcoma, Kaposi's
Katz, L N Myocardial infarction, observations on 100 patients who survived up to 6 years, 632
- Katz, L N—Continued
Survival after recent myocardial infarction, 305
Kelly, J J Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
Kidneys, pathogenesis of renal lesions in Bright's disease, 159
Kirsner, J B Gastroenterology, review of literature from July 1947 to July 1948, 321, 449
Gastroscopic and histologic appearance of gastric mucosa before and after vagotomy for peptic ulcer, 199
Klein, S P Periarthritis nodosa, study of chronicity and recovery, with report of 2 cases, 983
Koszalka, M F Hepatitis and its sequelae, including development of portal cirrhosis, observations on 100 cases, 782
Krainin, P Multiple myeloma with new bone formation, 976
Krumbhaar, E B Additional notes on Osler in Philadelphia, 26
Kussmaul-Maier Disease See Periarthritis nodosa
- Laennec's Disease See Liver, cirrhosis
Lanier, P F Sternal marrow in patients with metastatic cancer, 891
Laxatives See Cathartics
Legs See Extremities
Lerner, H B Hepatitis and its sequelae, including development of portal cirrhosis, observations on 100 cases, 782
Levine, B Clinical syndrome of occlusion of posterior inferior cerebellar artery, report of 3 cases, 431
Levy, H Traumatic coronary thrombosis with myocardial infarction, postmortem study, 261
Limbs See Extremities
Lincoln, C S, Jr Multiple hemorrhagic sarcoma and diabetes mellitus, review of series, with report of 2 cases, 738
Lindert, M C F Hepatitis and its sequelae including development of portal cirrhosis, observations on 100 cases, 782
Lipemia See Blood, fats and lipoids
Lipodystrophy, intestinal (Whipple's disease), 345
Lipids, fat and nitrogen absorption after folic acid administration in dogs deprived of external pancreatic secretion, 344
Literature See Books, Periodicals
Liver, anemia associated with cirrhosis of liver 958
cirrhosis, pathology of subchronic atrophy of liver, comparison with Laennec's cirrhosis, 933
Diseases See Hepatitis, Infectious
Longcope, W T Random recollections of William Osler, 1899-1918, 93
Lovejoy, F W, Jr Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
Lungs See also Respiratory Tract, etc
aureomycin therapy of nonpneumococcal and nontuberculous bacterial pulmonary infections, 875
clinical significance of bacteroides, 605
Embolism See Embolism
Lupus erythematosus, pathogenesis of renal lesions in Bright's disease, 159
Lymphocytes, hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
- McCann, W S Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
MacNalty, A S Osler at Oxford, 135
MacDermot, H E Osler's original autopsy books, 7
McGill Medical School, William Osler, "potent ferment" at McGill, 12

- Maier-Kussmaul Disease See Periarthritis nodosa
- Malformations See under names of diseases, organs and regions
- Manuals, manual on international exchange of publications, 520
- Marshall H C Gastroenterology, review of literature from July 1947 to July 1948, 321 119
- Maxillary Sinus, clinical significance of bacteroides 605
- Mayer, L D Barbiturate poisoning, report of 3 cases, 379
- Meckel's Diverticulum See Intestines, diverticula
- Medical Societies See Societies
- Medicine, medical arena in Toronto of Osler's early days in study of medicine, 2
- Military See Military Medicine
- Naval See Naval Medicine
- Psychosomatic See Mind body and mind
- Medin-Heine Disease See Pollomycellitis
- Megacolon See Colon, dilatation
- Meningitis, clinical significance of bacteroides, 605
- Mental Diseases See Psychiatry, etc
- Mershey, C Chronic nonleukemic myelosis, report of 6 cases, 277
- Mesentery, conditions involving mesentery 517
- massive resection of small intestine necessitated by mesenteric thrombosis 171
- Military Medicine See also Naval Medicine, etc
- war wounds and abdominal surgery, 517
- war wounds of rectum and anal sphincter, 506
- Mills G Y Myocardial infarction, observations on 100 patients who survived up to 6 years 632
- Survival after recent myocardial infarction 305
- Mind, body and mind, psychosomatic factors in gastrointestinal disease, 510
- Modern F W S Q Fever in veterans hospital, 917
- Mollerstrom, I Excretion of choline in urine of diabetic patients, 730
- Moolten S E Role of blood platelets in thromboembolism, 667
- Morphea See Scleroderma
- Motion Pictures, reviews 355
- Mouth, conditions of, 513
- Myeloma, multiple, with new bone formation 976
- Myelosis Aleukemic See Leukemia myelogenous
- myelogenous, chronic nonleukemic myelosis 277
- Myocardium See Heart
- Naval Medicine See also Military Medicine, etc
- medical aspects of submarine warfare, human factors as reflected in war patrol reports, 246
- Neel, J V Hematologic studies in Hiroshima and control city 2 years after atomic bombing 569
- Neoplasms See Cancer Sarcoma etc
- Nephritis, pathogenesis of renal lesions in Bright's disease, 159
- Nerves phrenic, motor manifestations of herpes zoster, report of case of associated permanent paralysis of phrenic nerve 407
- splanchnic, sympathectomy and splanchnicectomy 331
- vagus, anatomic variations of, their significance in vagus neurectomy, 322
- vagus, clinical results of vagotomy, 325
- vagus, gastroscopic and histologic appearance of gastric mucosa before and after vagotomy for peptic ulcer, 199
- vagus, historical aspects of vagotomy 322
- vagus, physiologic and other effects of vagus, vagotomy 321
- vagotomy, 323
- Neurology See also Nerves, etc
- and psychiatry, postgraduate course in, 356
- Nomenclature, chronic nonleukemic myelosis, report of 6 cases, 277
- Nomenclature, concepts of myocardial ischemia, 711
- tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases 845
- Nutrition See also Food, etc
- Intravenous, total intravenous alimentation, 509
- Oroya Fever, clinical manifestations of Carrion's disease 751
- Osler William, additional notes on Osler in Philadelphia, 26
- acquaintance, 86
- day with Dr Osler in Oxford, 143
- Dr Osler, scientist and teacher, 54
- Dr Osler's renal stones 40
- Dr Osler's use of time 51
- editorial on, 1
- excerpts from Osler, mosaic of bedside aphorisms and writings, 72
- gay of heart, 41
- hero worship, 104
- jocular side of Osler, 31
- medical arena in Toronto of Osler's early days in study of medicine 2
- my first medical clinic with Dr Osler, 81
- Osler at Oxford, 135
- Osler's original autopsy books 7
- Osler, recollections of undergraduate medical student at Johns Hopkins 77
- pathogenesis of renal lesions in Bright's disease 159
- posthumous tributes to Sir William Osler, 170
- random recollections of William Osler, 1899-1919, 93
- Sir William Osler, reminiscences, 110
- William Osler, humanist, 119
- William Osler in Philadelphia, 1884-1889, 18
- William Osler, a personal note 16
- William Osler, 'potent ferment' at McGill 12
- Osteomyelitis, clinical significance of bacteroides, 605
- Otitis Media clinical significance of bacteroides 605
- Oxford, day with Dr Osler in Oxford, 143
- Osler at Oxford, 135
- Packard, F R William Osler in Philadelphia, 1884-1889, 18
- Packard G L Aerosol and micronized ephedrine and penicillin therapy of diseases of lower respiratory tract treatment of bronchitis, bronchiectasis and intrinsic asthma, 389
- Pain See under Abdomen
- Palmer, W L Gastroenterology, review of literature from July 1917 to July 1948 321 419
- Gastroscopic and histologic appearance of gastric mucosa before and after vagotomy for peptic ulcer, 199
- Paralysis, Infantile See Pollomycellitis
- motor manifestations of herpes zoster, report of case of associated permanent paralysis of phrenic nerve, 907
- Periodic See Extrimites, paralysis
- Parasites, gastrointestinal, 460
- parasitic and diarrheal diseases, 150
- Paullin, T I My first medical clinic with Dr Osler 84
- Pearson, R Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
- Penfield, W Hero worship, 104
- Penicillin Therapy See Respiratory Tract, diseases
- Peptic Ulcer, clinical results of vagotomy, 325

- Peptic Ulcer—Continued
gastroscopic and histologic appearance of gastric mucosa before and after vagotomy for peptic ulcer, 199
physiologic and other effects of vagotomy, 323
phytobezoar in gastric stump, report of case and discussion of therapy, 824
ulcer of pyloric ring, report of 20 cases, 532
- Periarthritis nodosa, 983
nodosa, pathogenesis of renal lesions in Bright's disease, 159
- Pericardium, hemorrhage, spontaneous rupture of syphilitic aortic aneurysms of ascending aorta into pericardial cavity, with hemopericardium, report of sudden death in 29 cases, 540
- Perineum, pilonidal cysts, 516
- Periodicals, new, Interamerican review, 520
- Periodicals, new, Japanese Medical Journal 356
- Periodicals, new, Scandinavian Journal of Clinical and Laboratory Investigation, 520
- Peritoneum, conditions involving peritoneum, 516
- Phytobezoar See under Stomach
- Platelets See Blood, platelets
- Pneumococci, aureomycin treatment of pneumococcal pneumonia, clinical and laboratory studies on 33 patients, 857
- Pneumonia, aureomycin treatment of pneumococcal pneumonia, clinical and laboratory studies on 33 patients 857
(nonpneumococcal), aureomycin therapy of nonpneumococcal and nontuberculous bacterial pulmonary infections, 875
- Pollomyelitis virus, 459
- Polyp See Colon
- Porphyria See Porphyrin and Porphyrin Compounds
- Porphyrin and Porphyrin Compounds, acute porphyria, 519
development of porphyria in diabetes mellitus, report of 3 cases, 965
- Postgraduate Education See Education
- Pratt, J H Aequanimitas 86
- Pregnancy, clinical and biochemical study of remissions in nonspecific arthritis, report of case, 361
- Proctosigmoidoscopy See Colon
- Pruritus ani, 505
- Psychiatry and neurology, postgraduate course in, 356
- Psychosomatic Medicine See Mind body and mind
- Puberty, pernicious anemia in early adolescence, report of case in girl of 14, 445
- Purpura, Schonlein-Henoch, pathogenesis of renal lesions in Bright's disease, 159
- Pylorus, Ulcer See Peptic Ulcers
- Q Fever See Rickettsial Diseases
- Raaschou, F Pathology of subchronic atrophy of liver comparison with Laennec's cirrhosis 933
- Radiations See also Roentgen Rays
hematologic studies in Hiroshima and control city 2 years after atomic bombing, 569
Therapy, postgraduate courses on physics in radiation therapy at University of California, 355
- Rantz, L A Clinical significance of bacteroides, 605
- Rectum and anus 505
anorectal surgery, 506
extrinsic lesions of, 507
miscellaneous conditions 507
prolapse, 506
tumors of, 508
war wounds 506
- Reflex vasomotor, reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders, criticism of methods 396
- Respiratory Tract, diseases, aerosol and micronized ephedrine and penicillin therapy of diseases of lower respiratory tract treatment of bronchitis bronchiectasis and intrinsic asthma 389
- Rheumatic Fever, pathogenesis of renal lesions in Bright's disease, 159
- Ricketts, H T Development of porphyria in diabetes mellitus, report of 3 cases, 965
- Ricketts W E Clinical manifestations of Carrion's disease, 751
Gastroenterology, review of literature from 1947 to July 1948, 321 449
- Rickettsial Diseases, Q fever in veterans' hospital, 917
- Roentgen Rays, radiation injury, 490
- Roger's Disease See Heart, abnormalities
- Rosencrantz, E Posthumous tributes to Sir William Osler, 170
- Rosenthal, N Relation of pulmonary embolism to peripheral thrombosis, 410
- Salmonella infections, 453
- Sarcoma Kaposi's, multiple hemorrhagic sarcoma and diabetes mellitus, review of series, with report of 2 cases, 735
- Schistosomiasis, 469
- Schlichter, J G Dissecting aneurysms of aorta, 558
- Schonlein-Henoch Purpura See Purpura, Schonlein-Henoch
- Schools, school of medical illustration at University of Georgia School of Medicine, 356
- Scleroderma with gastrointestinal involvement, 351
- Selzer, A Defect of ventricular septum, summary of 12 cases and review of literature, 798
- Septum Interventricular See Heart
- Shapiro, S Relation of pulmonary embolism to peripheral thrombosis, 440
- Shigella See Dysentery
- Silver, M Development of porphyria in diabetes mellitus, report of 3 cases, 965
- Simon, A J Myocardial infarction, observations on 100 patients who survived up to 6 years, 632
- Sirek O V Excretion of choline in urine of diabetic patients, 730
- Smellin A Multiple myeloma with new bone formation, 976
- Smell, olfactory acuity and appetite, 509
- Snell F M Hematologic studies in Hiroshima and control city 2 years after atomic bombing 569
- Snodgrass H M Hepatitis and its sequelae including development of portal cirrhosis, observations on 100 cases, 782
- Societies, Biological Photographic Association 356
Chicago Society of Internal Medicine 837
Mississippi Valley Medical Society, 355
- Sodium Carboxymethylcellulose See Cathartics
- Solway A J L Dissecting aneurysms of aorta, 558
- Spirochaeta Pallida See Syphilis
- Spitzer, J M Relation of pulmonary embolism to peripheral thrombosis 440
- Splanchnicectomy See Nerves, splanchnic
- Sprue and steatorrhea, 342
- Steatorrhea See Feces, fat in, 342
- Sterling K Development of porphyria in diabetes mellitus, report of 3 cases 965
- Sternum, Puncture See Bones marrow
- Stomach See also Gastrointestinal Tract
mucosa, gastroscopic and histologic appearance before and after vagotomy for peptic ulcer, 199
phytobezoar in gastric stump, report of case and discussion of therapy, 824
Ulcers See Peptic Ulcer
- Stomatitis diagnosis and treatment 513
- Stools See Feces
- Streptomycin Therapy See Tuberculosis

- Submarines, warfare, medical aspects of, human factor as reflected in war patrol reports, 216
- Sulfonamides, Therapy See Colon diseases
- Surgery, war wounds and abdominal surgery, 515
- Sympathectomy, radiological changes in gastrointestinal tract of patient following Smithwick operation 331
- Symposiums, international symposium on high altitude biology, 836
- Syncope, tussive syncope, observations on disease formerly called laryngeal epilepsy with report of 2 cases, 845
- Syphilis, spontaneous rupture of syphilitic saccular aneurysms of ascending aorta into pericardial cavity, with hemopericardium, report of sudden death in 2nd cases, 540
- Terminology See Nomenclature
- Thorax See Heart, Lungs, etc
- Thrombopenia See Blood platelets
- Thrombosis, mesenteric 351
peripheral, relation of pulmonary embolism to 140
role of blood platelets in thromboembolism 667
traumatic coronary thrombosis with myocardial infarction, postmortem study 261
- Thyroid, clinical significance of bacteroides, 605
- Tongue glossodynia, 513
- Tropical Medicine See also under names of tropical diseases, as Sprue, etc
- Tuberculosis of intestines, 340
- Tumors See Myeloma Sarcoma, and under names of organs and regions as Colon, Duodenum, Rectum, etc
- Ulcers Duodenal See Peptic Ulcer
Peptic See Peptic Ulcer
- Umbilicus, endometriosis of, 518
- United Nations international symposium on high altitude biology, 836
manual on international exchange of publications 520
- Urinary Tract See also Kidneys
infections, clinical significance of bacteroides, 605
- Urine of diabetic patients excretion of choline in, 730
- Urology award 836
- Vagotomy See Nerves vagus
- Vasomotor System See Arteries, Blood pressure, Blood vessels, Sympathectomy, etc
- Veins See Blood vessels, Embolism, Thrombosis, etc
- Venereal Diseases See Syphilis
- Venous Pressure See Blood pressure
- Verruca Peruviana See Oroya Fever
- Vertigo, tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases 845
- Veterans, Q fever in veterans' hospital, 917
- Viruses See Herpes, Poliomyelitis Pneumonia, etc
- Volvulus See Colon
- Wroman, G M S Role of blood platelets in thromboembolism 667
- Wroman, L Role of blood platelets in thromboembolism, 667
- Wilk, L Phytobezoar in gastric stump, report of case and discussion of therapy, 524
- Wallenberg's Syndrome See Arteries cerebellar
- Wang H W Anemia associated with cirrhosis of liver 958
- War See also Military Medicine, Veterans, etc
medical aspects of submarine warfare human factor as reflected in war patrol reports 216
- Weinberg S J Aerosol and micronized ephedrine and penicillin therapy of diseases of lower respiratory tract treatment of bronchitis, bronchiectasis and intrinsic asthma, 359
- Welner M Relation of pulmonary embolism to peripheral thrombosis, 440
- Whipple's Disease See Intestines, diseases
- Wolarsky, W Chronic ulcerative colitis and carcinoma 293
- Xanthoma, tuberosum and coronary heart disease associated with hereditary hyperlipemia, study of 30 affected persons in family, 1002
- Yu P N G Tussive syncope, observations on disease formerly called laryngeal epilepsy, with report of 2 cases, 845
- Ziegler, D K Familial periodic paralysis, report on 2 families, with observations on pathogenesis of syndrome 419
- Zimdahl, W Intravenous catheterization of heart in suspected congenital heart disease, report of 72 cases 640

